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EFFICACY OF NEW DRUGS

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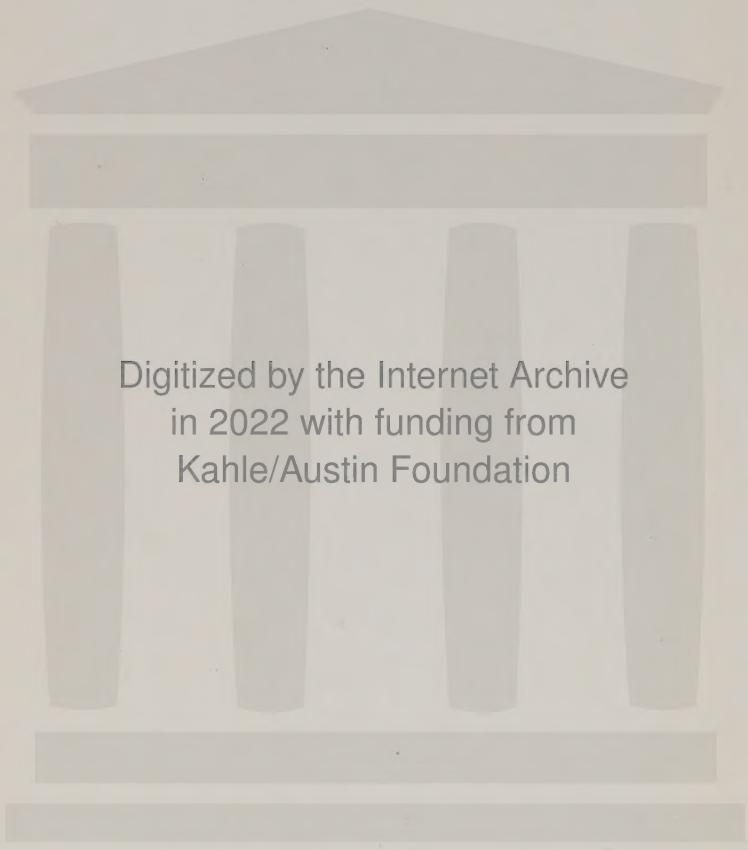
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THE MEDICAL CLINICS OF NORTH AMERICA

EFFICACY OF NEW DRUGS

HOWARD F. CONN, M.D., *Guest Editor*

Volume 51 — Number 5

SEPTEMBER, 1967

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Erratum

The apothecary dosage of atropine given on page 990 of the July 1967 issue was in obvious error. The sentence should read: Average clinical doses of atropine are 0.4 to 0.6 mg. (1/150 to 1/100 gr.).

RECENT SYMPOSIA

November, 1966 – *Nationwide*
HEMATOLOGIC DISORDERS

January, 1967 – *from Chicago*
VASCULAR DISEASES

March, 1967 – *Nationwide*
MODERN MANAGEMENT OF RESPIRATORY DISEASES

May, 1967 – *from Jefferson Medical College and Pennsylvania State University*
WHAT'S NEW IN INFECTIOUS DISEASES – PREVENTION AND IMMUNIZATION

July, 1967 –*from Ochsner Clinic*
UNUSUAL CLINICAL AND LABORATORY MANIFESTATIONS OF DISEASE

FORTHCOMING SYMPOSIA

November, 1967 – *Nationwide*
PSYCHIATRY FOR THE NONPSYCHIATRIST
RALPH KAUFMAN, M.D., *Guest Editor*

January, 1968 – *from Chicago*
PAIN AND ITS CLINICAL MANAGEMENT
JAMES E. ECKENHOFF, M.D., *Guest Editor*

March, 1968 – *from St. Louis*
ENDOCRINE DISORDERS
WILLIAM H. DAUGHADAY, M.D.,
THOMAS F. FRAWLEY, M.D., *Guest Editors*

May, 1968 –*Nationwide*
RHEUMATOID ARTHRITIS
JOHN BLAND, M.D., *Guest Editor*

July, 1968 – *from Mayo Clinic*
ROBERT E. SIEKERT, M.D., *Guest Editor*

NOTICE

Extraordinary efforts have been made by the authors, the editors and the publisher of this book to ensure that dosage recommendations are precise and in agreement with standards officially accepted at the time of publication.

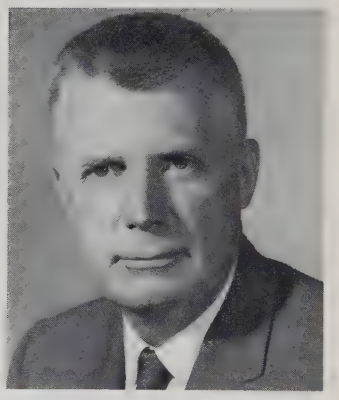
It does happen, however, that dosage schedules are changed from time to time in the light of accumulating clinical experience and continuing laboratory studies. This is most likely to occur in the case of recently introduced products.

It is urged, therefore, that you check the manufacturer's product information data for approved dosage, *especially if the drug to be administered or prescribed is one that you use only infrequently or have not used for some time.*

THE EDITORS

SYMPOSIUM ON THE EFFICACY OF NEW DRUGS

Foreword



This issue of *The Medical Clinics of North America* continues the series of new drug reviews published periodically since 1954. Topics have been selected because of current interest in a new product or because of new uses for older drugs. Authors have been chosen because of their active research in evaluation and testing of the agents discussed.

The testing of new therapeutic agents has become more specific and precise. Careful studies of effectiveness and adverse reactions must be carried out in great detail before the agent is released for use. But this testing cannot be considered as final. The true test comes after many patients have been given the drug. Unexpected adverse reactions and failure of effectiveness may appear at any time during the use of the agent. It is, of course, extremely difficult for the practicing physician to keep abreast of this ever changing flow of information. It is hoped the information contained in this volume will greatly assist the physician in his endeavor to prescribe the most effective therapeutic regimen for his patients.

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Newer Penicillins

WILLIAM J. MARTIN, M.D., F.A.C.P.*

Currently, there is available a wide variety of antimicrobial agents capable of eradicating the majority of uncomplicated bacterial infections. Among the available drugs, the semisynthetic penicillins represent a milestone in man's increasing ability to successfully combat a hostile environment. The purpose of this review is to provide a synoptic analysis of the semisynthetic penicillins and especially to attempt to indicate the current application in clinical situations.

For more than a decade, members of our group have periodically reviewed our experiences with antimicrobial drugs including the penicillins.[23-26, 28, 30, 31, 41] The penicillins are a group of antibiotics characterized by cross-allergenicity, the sharing of 6-aminopenicillanic acid (6-APA) as a nucleus, and exertion of a bactericidal effect on susceptible microorganisms. In addition to the naturally occurring penicillins, there is being produced an ever-growing number of semisynthetic penicillins.[25, 26]

The naturally occurring penicillins are produced by fermentation of several species of molds, such as Penicillium notatum and P. chrysogenum. Production of semisynthetic penicillins became possible on identification of the penicillin nucleus, 6-APA. The semisynthetic penicillins, and their clinical characteristics, reflect the chemical addition of different side chains to the 6-APA nucleus.

THE NATURAL PENICILLINS

Of the naturally occurring penicillins, penicillin G, penicillin O and penicillin V have been produced commercially. Penicillin G is preferred to penicillin V by most workers in more serious diseases. Penicillin O is no longer of clinical importance since it has become apparent that it is cross-allergenic with penicillin G. There are other natural penicillins such as F, K, N and X, which have no current clinical application.

In general, infections previously responding to the naturally occurring penicillins continue to respond, except those due to certain staphy-

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lococci. These natural penicillins currently are most commonly employed against streptococcal, pneumococcal, meningococcal, gonococcal, and syphilitic infections. Infections due to numerous other organisms such as anthrax bacilli, Actinomyces israeli, Pasteurella multocida (septica), Erysipelothrix insidiosa (rhusiopathiae), and Listeria monocytogenes have been treated successfully with these drugs.

THE SEMISYNTHETIC PENICILLINS

The natural penicillins have chemical structures so complex that for many years they eluded identification. In 1957 Sheehan created penicillin V in the laboratory, and in 1958 he produced minute quantities of the nucleus of the penicillin molecule, 6-APA, which is a fused beta-lactamthiazolidine ring system, bearing a carboxyl group at carbon 3 and an amino group at carbon 6. Important was the discovery that the mold P. chrysogenum, which produces the natural penicillins, produces the nucleus before attachment of the side chains. Also discovered was a method to inhibit the attachment of the naturally occurring side chains; thus production of the mold could be stopped at the point at which only the unattached nucleus had been produced. The fermentation process was scaled up in order to produce 6-APA in large quantities, and organic chemists began adding various side chains. An alternative method for producing 6-APA is employment of amidase (acylase) enzymes to remove the side chain from readily obtainable penicillins. These penicillinamidases or penicillinacylases are of fungal and bacterial origin.[12] Thus, it became possible to semisynthesize new penicillins that reflected variations in the attached side chains. The first commercial example of this ability was phenethicillin, but a more monumental accomplishment was the semisynthesis of the penicillinase-resistant methicillin in 1960 by Doyle. Further search has led to oxacillin, ampicillin and the other semisynthetic penicillins. These drugs appear to be only bellwethers of even newer semisynthetic penicillins that have possible clinical application.

PHENETHICILLIN OR PHENOXYETHYL PENICILLIN. Like penicillin V,[29] phenethicillin (Syncillin, Darcil, Maxipen, Semopen)[27] is resistant to gastric acid. However, in contradistinction to potassium penicillin V, the absorption of phenethicillin from the intestinal tract is more likely to be reduced when the drug is taken with food or shortly after food has been consumed. Phenethicillin may produce higher serum levels than penicillin V, but the experience at our clinic indicates that there is, weight-for-weight, no difference in the antibacterial effect of the drugs, as indicated by serum bactericidal tests. Therefore, the practitioner may use potassium penicillin V and the semisynthetic phenethicillin more or less interchangeably, remembering that phenethicillin should be given when the stomach is empty. Phenethicillin, like penicillin V, is inactivated by penicillinase; binding of the two drugs by serum protein is similar and amounts to about 75 per cent. Phenethicillin, like penicillin V, is used in mild to moderately severe infections due

to susceptible organisms and is given in a similar dosage: 125 mg. (200,000 units) to 250 mg. usually is given at 4- to 8-hour intervals, but 500 mg. or more has been given even more frequently.

Methicillin. Methicillin (Staphcillin, Dimocillin-RT)[1, 13] can be employed against penicillin G–resistant staphylococci, because it is not appreciably inactivated by staphylococcal penicillinase. That is to say, methicillin is capable of eradicating staphylococci which, on in vitro testing, require more than 1.0 μg. of penicillin G for inhibition. Compared with penicillin G, however, methicillin has a narrow range of effectiveness and less antibacterial activity. At best, it is only about a third as effective as penicillin G against pneumococci and group A streptococci; like other available penicillinase-resistant penicillins, methicillin is virtually without effect against enterococci. The drug is unsuitable for oral administration and is given intravenously or intramuscularly. Serum levels reach a peak about ½ to 1 hour after intramuscular administration. With single doses, serum concentrations decrease rapidly and may decline below the therapeutic range after 3 to 4 hours. Nearly half the injected dose is excreted in the urine within the first 6 hours after administration; like the natural penicillins, methicillin is excreted chiefly via the renal tubules. In patients with renal insufficiency, methicillin may persist in serum for 10 hours or longer. In very young infants, apparently because of inadequate renal reserve, the excretion of the penicillins (including methicillin) may be delayed for days, and a correspondingly high and sustained blood concentration may be present. Serum levels are not appreciably influenced by hemodialysis. Approximately 20 per cent of methicillin is bound to plasma protein.

The mechanism of penicillinase resistance of methicillin and allied drugs is not known, but presumably the side chains of these penicillins prevent the splitting of the beta-lactam ring of the 6-APA nucleus. It is theorized that the two methoxy groups attached to the benzene ring in the side chain of methicillin may disallow effective contact by the enzyme, and this theory has been referred to as that of "steric hindrance."

Strains of Staphylococcus aureus isolated from clinical material in British hospitals have been described as being resistant to the drug, and drug-tolerant strains also have been produced in the laboratory.[2, 6, 14, 38, 48] Because staphylococci have demonstrated their ability to develop resistance to methicillin, there is fear that indiscriminate use of the drug and of those allied agents against which these staphylococci may demonstrate cross-resistance[2] will lead to an increase in such resistant strains.

Methicillin is given intravenously by intermittent injection in amounts of 1 to 2 gm. every 2 to 6 hours; when dissolved in 20 to 30 ml. of distilled water, the drug can be injected directly into the vein or via intravenous tubing. Some workers dissolve the drug in 100 to 250 ml. of distilled water and administer it "piggy back" through intravenous tubing. Methicillin should not be added to large quantities of infusion fluids, which are often sufficiently acid to cause inactivation over several hours; nothing should be added to solutions of methicillin since the drug

is destroyed by addition of certain other agents, including kanamycin. When administered intramuscularly, the drug is usually given in amounts of 0.5 to 1 gm. every 4 to 6 hours; 1 gm. can be injected in about 1.5 ml. of distilled water. Persistence of infection despite optimal therapy has been noted.

Intrapleural and intra-articular injections of 0.5 to 1 gm. of methicillin, dissolved in 5 to 10 ml. of sterile normal saline, have been given daily in patients with pertinent infections. Methicillin also has been administered as an aerosol to combat selected staphylococcal infections of the lung; 500 mg. of the drug can be dissolved in about 3 ml. of distilled water and inhaled over a period of about 20 minutes four times daily using a pump and nebulizer. Methicillin has been used in the form of eye drops or eye ointment at a 1 per cent concentration.

OXACILLIN. Like methicillin, oxacillin (Prostaphlin, Resistopen)[10, 16, 43, 45] is penicillinase-resistant, but in addition oxacillin is relatively acid-resistant and can be given orally as well as parenterally. Although oxacillin is less resistant to staphylococcal penicillinase, being destroyed at about twice the rate of methicillin, the antibacterial action of oxacillin is considerably greater than methicillin against susceptible organisms. Strains of S. aureus isolated from clinical material and resistant to methicillin may show a corresponding increase in resistance to oxacillin,[2] cloxacillin[2] and nafcillin.[38]

When oxacillin is given orally in a single dose, peak serum levels occur in different persons after intervals varying from ½ hour to 2 hours. Food appears to interfere with the absorption of oxacillin and decreases serum levels. Considerable variation in serum levels and their duration follows oral administration of the drug; in some patients, no drug activity in serum can be demonstrated. Such erratic serum levels have considerably tempered initial enthusiasm for oral use of the drug. As a generalization, after oral administration, the serum levels of oxacillin persist for about 4 hours. In contradistinction to methicillin, in patients having renal insufficiency, the persistence of oxacillin in the serum may be only slightly prolonged. With intramuscular administration, peak serum levels usually occur in ½ hour; 0.5 gm. given intramuscularly produces blood levels comparable to those obtained on administration of 1 gm. by mouth. Significant accumulation appears not to occur with recommended doses every 4 hours by either the oral or the intramuscular route. After intravenous administration, levels of oxacillin in blood are higher than after intramuscular injection, but decline more rapidly, that is, in less than 4 hours. Serum levels of oxacillin are not appreciably affected by hemodialysis. Oxacillin and the allied drug cloxacillin are bound to serum proteins to a greater degree (80 per cent or more) than are other commercially available penicillins, but the exact significance of this is not known.

As in therapy with methicillin, the prime indication for use of oxacillin is selected infections caused by penicillin G–resistant staphylococci. Oxacillin has cured serious staphylococcal infections, and thus one should avoid its indiscriminate use in an attempt to limit staphylo-

coccal resistance to it and allied drugs. Of possible ominous significance in this regard is the fact that resistance to the drug by strains of staphylococci is readily induced in the laboratory.

Oxacillin is five to eight times more effective than methicillin against penumococci and susceptible streptococci but is not so effective as penicillin G on a milligram-for-milligram basis. While oxacillin is not the drug of choice for the treatment of infection due to these organisms, when given in doses sufficiently large to inhibit penicillinase-producing staphylococci, it may be capable of controlling an associated pneumococcal infection and most streptococcal infections. Some workers believe it may be unnecessary to give penicillin G conjointly to control infections which might be due to pneumococci and most streptococci before microbiologic data are reported. However, it is advisable to use penicillin G or V in proved pneumococcal or streptococcal infections. The drug is ineffective against Streptococcus faecalis. As has been true of methicillin, persistence of infection has been noted despite administration of optimal amounts of oxacillin.

Oxacillin does not appear to be excreted in sweat, does not diffuse readily into the various body cavities, and is not likely to be present in substantial amounts in body fluids. The renal excretory route of oxacillin, like penicillin G and methicillin, appears to be chiefly tubular. The extrarenal inactivation of oxacillin seems to be greater than that of methicillin. The higher biliary excretion rate of oxacillin, compared to methicillin, may account for the lower urinary recovery of oxacillin.

For moderately severe infections, oxacillin is given in oral doses of 1 gm. four to six times daily, preferably when the patient has an empty stomach; this dosage may be reduced to 0.5 gm. once improvement occurs or for therapy of milder infections. The usual daily intramuscular dose also is 0.5 to 1 gm., given every 4 to 6 hours. In severe infections, oxacillin is administered intravenously every 2 to 6 hours in amounts of 1 to 2 gm. dissolved in 10 to 20 ml. of 5 per cent dextrose or normal saline solution injected over several minutes. As an alternative method for intravenous use, the drug can be dissolved in 100 to 200 ml. of an isotonic solution and given for 1 or 2 hours. Oxacillin is more resistant than methicillin to deterioration in solutions prepared for intravenous administration.

NAFCILLIN. In contradistinction to the isoxazolyl penicillins, nafcillin (Unipen)[19, 22, 36, 43] has an ethoxynaphthyl side chain. On oral administration, nafcillin produces serum levels that may be lower than those attained with oxacillin, but nafcillin persists longer in the serum and provides better tissue penetration. Like oxacillin, nafcillin is absorbed poorly by the oral route in some persons. Serum levels of nafcillin are higher after oral administration, when the subject is fasting, or has had repeated doses. After oral administration, peak serum levels of nafcillin are attained within 1 to 2 hours; after intramuscular injection they are attained in 30 minutes. Serum binding of nafcillin amounts to about 60 per cent and therefore is less than that with oxacillin and cloxacillin but greater than that with methicillin.

In vitro, nafcillin is considerably more active than methicillin, somewhat more active than oxacillin, but less active than penicillin G against susceptible organisms. However, in vivo, nafcillin appears to be at least as effective against penicillin-resistant staphylococci as is methicillin, oxacillin or cloxacillin.

Because nafcillin persists longer in serum and tissues than does methicillin or oxacillin, it may have special application in selected chronic infections, such as those of the bones and joints.

As was mentioned in the case of oxacillin, since nafcillin appears to be quite active against pneumococci and most streptococci, it has been suggested that penicillin G need not be given conjointly with nafcillin as "coverage" against these possible pathogens while one awaits the report of definitive microbiologic data. Like methicillin, oxacillin and cloxacillin, it is ineffective against enterococci.

Despite the availability of similar drugs, including cloxacillin, continued availability of nafcillin, especially preparations of the drug for parenteral administration, appears desirable because of the concentration and persistence of nafcillin attained in the body tissues.

The usual oral dose of nafcillin is 0.5 to 1 gm. every 4 to 6 hours in the fasting state. When nafcillin is administered intramuscularly, 0.5 to 1 gm. also is given every 4 to 6 hours. A dose of 1 to 2 gm. has been given intravenously every 2 to 6 hours in the manner previously noted for oxacillin.

CLOXACILLIN. Cloxacillin (TegoPen)[17, 20, 47, 51] is suitable for oral administration and is active against susceptible gram-positive pathogens. Cloxacillin differs chemically from oxacillin only in that it has a chlorine atom in its structure. As is true for oxacillin, strains of S. aureus isolated from clinical material and resistant to methicillin have been described as being resistant to cloxacillin.[2] Unlike methicillin, cloxacillin is less effective against a large inoculum than against a small one, probably because the drug is less resistant to staphylococcal penicillinase than is methicillin. On in vitro testing, cloxacillin is less active than penicillin G, 5 to 10 times more active than methicillin, and about twice as active as oxacillin. Serum levels after oral administration of cloxacillin are higher and more predictable than those after the use of oxacillin, but cloxacillin may be more rapidly excreted; nevertheless, with comparable doses the serum antibacterial activity of cloxacillin is superior to that of oxacillin. Cloxacillin is best absorbed when taken in the fasting state; however, orally administered doses may be absorbed only to a limited extent or not at all. After oral administration, peak serum levels of cloxacillin usually are attained in about 1 hour and persist 4 to 6 hours.

Like oxacillin, the drug is bound to plasma proteins to the extent of 85 to 90 per cent.

On intramuscular administration, cloxacillin, oxacillin and nafcillin appeared to be equally active when absorption, serum antistaphylococcal activity and serum binding were all combined in a single assay method.[43] Peak serum levels of cloxacillin after intramuscular admin-

istration occur in approximately 1 hour. As is true of oxacillin, serum levels after intramuscular administration of cloxacillin are approximately twice those obtained with a similar oral dose. It is to be noted that as of this writing only the preparation for oral use is commercially available in the United States, and that parenteral administration of cloxacillin remains investigational.

While cloxacillin has been effective in various infections due to penicillin G–resistant staphylococci, as has been true also of methicillin and oxacillin, instances of refractoriness to optimal therapy have been observed.

If further clinical use of cloxacillin fails to reveal increased comparative toxicity, it may replace oxacillin for oral use, since the antibacterial activity of cloxacillin is greater than that of oxacillin and the newer agent provides levels in the blood superior to those achieved on administration of oxacillin. The oral dose of cloxacillin varies from 0.25 to 1 gm. given every 4 to 6 hours in the fasting state.

Ampicillin. Ampicillin (Polycillin, Penbritin)[18, 21, 39] is an orally and parenterally administered agent, which has an anticoccal effect and also is effective against strains of gram-negative bacilli. Ampicillin has an alpha-aminobenzyl group in place of the benzyl side chain of penicillin G. More than 80 per cent of strains of Escherichia coli appear to be susceptible to ampicillin. About 90 per cent of strains of Proteus mirabilis appear to be sensitive to the drug. Ampicillin also is active against strains of Salmonella, Shigella, Haemophilus influenzae, Haemophilus parainfluenzae, Brucella and some species of Bacteroides. Susceptible gram-negative bacilli are inhibited by feasible levels of ampicillin in serum, that is, 5 μg. of the drug per ml. or less. However, it is ineffective against most strains of Proteus organisms that are indole-positive and against the majority of Klebsiella-Aerobacter and Pseudomonas organisms. Resistant strains of bacteria, such as E. coli, have emerged in clinical material.

Like penicillin G, ampicillin is inactivated by staphylococcal penicillinase and hence has no application in the management of infections due to penicillin G–resistant staphylococci. As a generalization, ampicillin is somewhat less active than penicillin G against pneumococci, many streptococci, and Clostridium organisms. However, ampicillin and phenethicillin show greater in vitro activity against enterococci than do the other semisynthetic penicillins discussed herein. Also, ampicillin appears to have an antienterococcal effect even greater than that of penicillin G. Ninety per cent or more of strains of enterococci are susceptible in vitro to ampicillin; streptomycin or kanamycin may enhance the antibacterial effect of ampicillin against enterococci.

Being stable in gastric juices, ampicillin is suitable for oral use. Levels of ampicillin in serum and urine do not appear to be greatly lessened when the drug is taken along with food. After oral administration, peak levels in serum are reached in about 2 hours and trace levels are present for at least 6 hours. When the drug is given intramuscularly, peak levels in serum are achieved in ½ to 1 hour, and the levels are

considerably higher and more prolonged. Intravenous injection of ampicillin produces higher peak levels in the serum and more rapid excretion of the drug than does intramuscular administration. In patients having renal insufficiency, the duration of serum concentrations of ampicillin may be half again as long as those in normal subjects. Ampicillin is bound to plasma proteins only to the extent of about 10 per cent. The concentration of the drug in the bile may be 300 times that in the plasma. High concentrations of ampicillin also appear in the urine.

Ampicillin appears to have eradicated H. influenzae from the respiratory tract of patients having chronic bronchitis and has been effective in pneumonia caused by this organism. It is being investigated as a single drug in the management of bacterial meningitis in children prior to the report of microbiologic studies. Initial results indicate that response to ampicillin compares favorably with that after use of chloramphenicol in influenzal meningitis and with that after administration of penicillin G in meningococcal and pneumococcal meningitis.[3, 32] Urinary infections and bacteremia caused by strains of E. coli, P. mirabilis, and enterococci have responded to ampicillin. There are preliminary indications that in enterococcal bacteremia and endocarditis, ampicillin may approach the efficacy of combined streptomycin-penicillin G therapy.[4, 37] Ampicillin might be preferred to the tetracyclines under certain circumstances, as in pregnant women and infants, in order to avoid tetracycline-induced adverse reactions which are particularly apt to occur in such patients. Ampicillin appears not to have as yet displaced chloramphenicol as the drug of choice in typhoid fever, but the relapse rate after use of ampicillin may be lower. In patients with other Salmonella infections, results are regarded as comparable to those obtained with previously available agents. Fecal or urinary excretors of Salmonella organisms are more likely to respond to ampicillin therapy than are biliary excretors; biliary excretors without cholelithiasis respond better than those with stones, but after cholecystectomy at least half will respond.[44] Good results also have been described in cases of dysentery from Shigella organisms. Ampicillin also has been recommended as an alternative drug to the tetracyclines in the management of intestinal malabsorption[15] and in the treatment of pertussis.[35]

A dose of 0.5 to 1 gm. of ampicillin is given every 4 to 6 hours orally. It is often given parenterally in the same dosage, but higher doses are not uncommon. It is to be noted that the stability of sodium ampicillin may decrease markedly with increases in its concentration, and also that it is hazardous to store injection solutions. Even when solutions are stored at refrigeration temperatures, 5 to 25 per cent of the initial potency of the drug may be lost within a few hours. The presence of dextrose and lactate in solutions of ampicillin may further accelerate loss of the drug's potency.

A dose of 500 mg. of ampicillin dissolved in 5 to 10 ml. of sterile normal saline has been given by intrapleural and intra-articular injection. Ampicillin also has been used in the form of eye drops or eye ointment in a 1 per cent concentration.

Other semisynthetic penicillins currently are undergoing clinical investigation; examples of these are dicloxacillin and hetacillin.

DICLOXACILLIN. Like oxacillin and cloxacillin, dicloxacillin[34] is one of the isoxazolyl group of semisynthetic penicillins, but dicloxacillin is not commercially available in the United States. Dicloxacillin differs from cloxacillin in having an additional chlorine in the side chain of the phenyl ring. The ability of dicloxacillin to resist gastric acid is similar to that of cloxacillin. There are preliminary indications that methicillin-resistant staphylococci, which means organisms that may also resist oxacillin, cloxacillin and nafcillin, may be inhibited by dicloxacillin.[11, 34] Thus, in infections due to staphylococci that resist the commercially available antistaphylococcal penicillins, dicloxacillin might have special application. As a generalization, on oral and parenteral administration of dicloxacillin, serum levels appear to be twice as high as those after cloxacillin use and four times those of oxacillin. However, the antibacterial activity of dicloxacillin in the presence of human serum may be more depressed than that of cloxacillin. Increasing the oral dosage of dicloxacillin to more than 500 mg. may not produce a proportional increase in the serum level. In the fasting state, oral doses produce significant serum levels that persist about 4 hours; when such doses are taken with food, the levels may persist for 6 hours. Although serum levels after intramuscular administration of dicloxacillin may not be greatly higher and may be only slightly more prolonged than after its oral administration, they are more reliable. Intravenous administration of dicloxacillin produces higher initial levels in serum that those that occur after intramuscular injection, but the drug is eliminated more rapidly and consequently is given every 4 hours or more, often by the intravenous route. Serum binding of dicloxacillin is similar to that of oxacillin and cloxacillin. After oral administration, 50 per cent or more of the dose is excreted in the urine in 6 hours.

Studies in human staphylococcal infections appear to indicate that dicloxacillin is at least as effective as the commercially available penicillinase-resistant penicillins.

The usual oral and intramuscular dose of dicloxacillin is 0.25 to 0.5 gm. given every 4 to 6 hours. Doses of 1 gm. or more have been given every 2 to 4 hours intravenously.

HETACILLIN. This drug is derived from an acylation condensation procedure in the synthesis of ampicillin. Hetacillin is absorbed from the gastrointestinal tract, and on absorption, some data indicate that it may be reconverted to ampicillin by hydrolysis. Hetacillin and ampicillin have similar antibacterial spectra and appear to have at least comparable potency; like ampicillin, hetacillin is hydrolyzed by penicillinase. When each drug is given orally in equal doses, the serum levels of hetacillin exceed those of ampicillin after the fourth hour. When given intravenously, hetacillin is said to produce serum concentrations considerably higher than those after injection of ampicillin. The renal clearance of hetacillin is similar to that of ampicillin, and the appearance in the urine of a larger proportion of the administered dose of hetacillin has

been taken to indicate an even greater resistance to extrarenal destruction than is true for ampicillin.[50] It is conceivable that in the future, hetacillin may be preferred to ampicillin because of hetacillin's better utilization in humans. Hetacillin has been effective in bacteremia due to E. coli, pneumonia due to Diplococcus pneumoniae and H. influenzae, urinary infections due to susceptible gram-negative bacilli, shigellosis and salmonellosis. It has been concluded that 6 gm. of hetacillin per day should be therapeutically equivalent to 8 gm. of ampicillin.[50]

PRESENT STATUS OF THE SEMISYNTHETIC PENICILLINS

The precise application of the individual semisynthetic penicillins cannot be currently evaluated, and problems of their evaluation undoubtedly will be increased on discovery of still newer derivatives that have possible clinical use. However, it is clear that methicillin, oxacillin and nafcillin are efficacious in the parenteral therapy of serious infections caused by penicillin G–resistant staphylococci. Also, oxacillin, cloxacillin and nafcillin, because of their stability in acid, are effective drugs on oral administration in milder infections due to these organisms; of the three, cloxacillin may be preferable because of the more reliable serum levels attained. The commercially available penicillinase-resistant penicillins have been responsible for reducing considerably the mortality rate in cases of staphylococcal pneumonia and have been effective in at least 50 per cent of cases of staphylococcal endocarditis due to penicillin G–resistant organisms. In addition, with these penicillins, a cure rate as high as 70 per cent in some series of staphylococcal bacteremia has been reported.[25] Many other staphylococcal infections, such as those of the skin, skeletal system and urinary tract, have been eradicated by these drugs. Despite these remarkable achievements by the penicillinase-resistant penicillins, the overall mortality rate after their use in patients with severe staphylococcal infections is between 30 and 40 per cent. This mortality appears largely to reflect underlying factors in the host responsible for the susceptibility to, as well as the severity of, the infection. In severe staphylococcal infections, such as endocarditis, doses of 8 to 24 gm. per day or greater usually are necessary for cure, and treatment should be given for at least 3 to 4 weeks.

The effectiveness of a penicillinase-resistant penicillin depends on at least two properties: (1) the inherent antistaphylococcal potency of the individual drug, and (2) the degree to which the drug resists the effects of penicillinase. The ultimate clinical potential of a given drug will be influenced by multiple factors, of which these two properties, while important, probably represent only initial considerations. An additional important factor in this regard undoubtedly will be the comparative incidence of untoward effects that follow use of the individual drugs, and which may become evident only after more prolonged observation.

Among the currently available data of clinical importance regarding the antistaphylococcal semisynthetic penicillins, the following are

worthy of emphasis. As a generalization, these agents should be used only in selected clinical situations wherein staphylococci demonstrate resistance to penicillins G and V on in vitro testing or infection due to such pathogens is likely and "coverage" is indicated while microbiologic data remain unreported. These drugs should not be used, without special investigations and precautions, in patients who have had allergic reactions to other penicillins, since cross-allergenicity is known; as with other penicillins the antistaphylococcal semisynthetic penicillin should not be used in patients who have other allergies, particularly asthma, unless the need is overriding.

A higher concentration of these drugs in serum is required to exert a comparable bactericidal effect than is necessary with penicillin G, since the agents, although bactericidal, are less so than penicillin G, weight-for-weight, in vitro. However, since the minimal inhibitory concentrations of oxacillin, cloxacillin and nafcillin against pneumococci and streptococci (excepting enterococci) are relatively close to those of penicillin G, some investigators have concluded that it is acceptable to give one of these drugs as a single agent in infections in which either staphylococci or one of the aforementioned cocci is an etiologic possibility and before microbiologic data are available. In other words, these workers believe that conjoint use of penicillin G or V may be unnecessary under such circumstances, but when the pathogen and its in vitro susceptibilities are known, one can then switch to a natural penicillin or continue the semisynthetic penicillin, accordingly. This generalization, if supported by results of continued investigation, would appear particularly applicable, while one awaits results of microbiologic studies, to infections of a serious nature (possibly due to staphylococci) that originate in a hospital.

The indiscriminate use of the semisynthetic penicillins must be avoided; otherwise, since the degree of resistance to an agent is related to the amount of the drug being used in a geographical area, and since cross-resistance among the drugs to some bacterial strains has been demonstrated,[2] the incidence of resistant strains probably will increase. Also, with cross-allergenicity among the penicillins, indiscriminate use of the semisynthetic agents will contribute further to the problems of allergy to penicillin – a problem that is already sizable.

Because bacterial endocarditis continues to be a serious complication of open heart surgery, especially when intracardiac prostheses are used, the prophylactic administration of a penicillinase-resistant penicillin to such patients is being investigated by various groups. While delayed infection may sometimes occur from exogenous sources, in most cases it appears to reflect contamination at surgery. Administration of such a drug for 12 to 24 hours before operation and no longer than 72 hours after it is recommended by some workers in order to avoid undue disturbance of the normal microflora and consequent enhancement of superinfection by resistant organisms on the valve or elsewhere in the body. Conjoint administration of streptomycin usually is not advised, since there is little evidence that an enhanced antibacterial effect is thereby achieved, and the likelihood of streptomycin-susceptible

gram-negative bacillary infection is remote. Of course, use of a penicillinase-resistant penicillin in this manner will not protect against naturally resistant strains of coagulase-positive staphylococci; of greater theoretic concern is the finding that coagulase-negative strains appear more likely to emerge as being resistant to such drugs, and these staphylococci are not an uncommon cause of postcardiotomy endocarditis. It has been theorized that simultaneous use of another antistaphylococcal drug such as cephalothin would give broader coverage against resistant staphylococci, but contrariwise, cephalothin by its effect on the microflora might further enhance the incidence of postoperative infection due to such organisms as Bacteroides and Pseudomonas. Prophylactic use of a penicillinase-resistant penicillin is also being investigated by some workers in selected neurosurgical and orthopedic procedures.

Oxacillin, cloxacillin and nafcillin are more effective on a weight basis than methicillin against penicillinase-producing and nonpenicillinase-producing gram-positive organisms, and consequently the question has been raised whether continued availability of methicillin is necessary. Also, use of oxacillin appears to be associated with a decreased likelihood of nephrotoxicity, hematotoxicity and superinfection. However, on comparison with methicillin, oxacillin does not appear to be excreted in sweat, does not diffuse readily in the various body cavities, and is not likely to be present in substantial amounts in body fluids. In this same regard, it is conceivable that oxacillin in turn might be replaceable by cloxacillin for oral therapy, because the latter is more active and provides higher and more predictable blood levels. Nafcillin continues to be preferred in certain situations because of its more persistent levels in serum and especially in tissues.

If one is an adherent to the concept that the extent of a drug's binding to body protein indicates its ability to inhibit bacterial growth, or the lack of it, one should recall that dicloxacillin, cloxacillin and oxacillin are highly bound, and nafcillin is bound to an intermediate degree, while methicillin is least bound. Although some workers have indicated that a drug highly bound to protein may be less available for bacterial inhibition, it is also conceivable that this union may sequester the drug's antibacterial action and thereby prolong its effect.

Of the semisynthetic penicillins which are destroyed by penicillinase, phenethicillin is used more or less interchangeably with penicillin V, but in contradistinction to potassium penicillin V, the intestinal absorption of phenethicillin is more likely to be reduced when it is taken in association with food. Because ampicillin has been proved effective in such serious infections due to gram-negative bacilli as influenzal meningitis, bacteremia due to E. coli, and systemic salmonellosis, it consequently has a more assured niche in the current therapeutic armamentarium.

A METHOD OF ANTISTAPHYLOCOCCAL MANAGEMENT

As a generalization, current treatment of staphylococcal infections is determined largely from results of in vitro susceptibility tests. It

might be well to reiterate that the belief which equates coagulase-positivity with staphylococcal pathogenicity and relegates coagulase-negative staphylococci to the position of harmless saprophytes is fallacious. Coagulase-negative staphylococci are a not uncommon cause of bacterial endocarditis, including postcardiotomy cases, and of meningitis in patients who recently have had ventricular shunt procedures. In various hospitals 20 to 40 per cent of pathogenic strains of coagulase-negative staphylococci resist the action of penicillin G.

In the following scheme, an attempt is made to include all available antistaphylococcal drugs and to indicate their possible clinical application. It is obvious that some of these drugs are infrequently employed at present, and for this reason, it is conceivable that in the future some of them may be withdrawn from commercial use. In this regard, it is common experience that the unavailability of microbiologic data, especially the results of in vitro susceptibility tests, often results in use of a given drug and its continued use thereafter when the patient responds well. If such data were more speedily reportable, perhaps some of the potentially effective drugs in a given situation would be employed, and one would be less concerned about emergence of bacterial strains resistant to the drugs more commonly used at present.

If staphylococci are susceptible on in vitro tests to penicillins G and V, these remain the drugs of choice; in mild infections, orally administered penicillin V has been successful. As mentioned previously, penicillin V and the semisynthetic phenethicillin can be used more or less interchangeably. In more than half the patients without hospital contact, penicillins G and V remain effective and the drugs of choice in staphylococcal infections. When susceptibility tests indicate that a Staphylococcus resists penicillins G and V but is sensitive to methicillin or a kindred drug and to other antibacterial agents, selection of the appropriate agent depends on (1) the nature of the infection and the need for a bactericidal effect and (2) considerations of comparative toxicity and convenience of administration. Using these criteria, one may roughly divide staphylococcal infections into three groups in attempting to indicate the clinical potential of the penicillinase-resistant semisynthetic penicillins.

In the first group, the outstanding entity is staphylococcal bacterial endocarditis. In such endocarditis resistant to penicillin G, one of the penicillinase-resistant semisynthetic penicillins is preferred, since they appear to be at least as effective as the more recently introduced cephalothin. Also they are less toxic than other bactericidal agents such as vancomycin, kanamycin and ristocetin. It is generally accepted that eradication of staphylococcal bacterial endocarditis requires use of agents capable of bactericidal effect. Also use of methicillin or an allied agent is less cumbersome than combined antibiotic therapy with the so-called bacteriostatic agents such as erythromycin, novobiocin and chloramphenicol (which are generally considered to be ineffective when used alone in bacterial endocarditis) together with such bactericidal agents as bacitracin and kanamycin.

Methicillin and kindred drugs are effective agents in bacterial endo-

carditis, and although they are bactericidal, one should recall that they are less bactericidal, weight-for-weight, than penicillin G. The doses recommended for these agents, when they first became available, were considerably smaller than those that have been employed in therapy with penicillin G. More recently, however, by intermittent intravenous therapy through the tubing of continuously administered parenteral fluid, 2 gm. or more has been given every 2 to 4 hours so that more comparable total dosage has been possible. In patients allergic to the penicillins, some workers favor use of cephalothin over vancomycin, but the latter agent does have the virtue of established efficacy.

In the second group of staphylococcal infections are included such diseases as bacteremia, meningitis, pneumonia, internal abscesses, peritonitis, mastoiditis, bacterial arthritis and selected severe infections of the urinary tract. If one accepts bacteremia as typical of this group, it is seen that the need for agents with the potential of methicillin and kindred drugs is not so great in this group as in bacterial endocarditis. Erythromycin and novobiocin have been effective in staphylococcal bacteremia; against susceptible strains, these agents have been about as effective as penicillin G had been prior to the emergence of penicillin G–resistant strains. Since erythromycin and novobiocin can be given orally and are relatively nontoxic, and since one wishes to minimize the use of methicillin and allied agents so as to minimize in turn staphylococcal resistance to them, there are several reasons why the newer synthetic penicillins may not be automatically the agents of choice in these infections. Lincomycin may fall into the same category as erythromycin and novobiocin. If erythromycin, novobiocin or lincomycin is not applicable, one might consider cephalothin, bearing in mind it has to be given parenterally and that in some cases it does not eradicate an infection despite in vitro bacterial susceptibility to the drug.

However, it seems reasonable to use a penicillinase-resistant semisynthetic penicillin before considering the use of more toxic agents such as vancomycin, kanamycin, chloramphenicol or ristocetin, or combined therapy, in about that order of choice.

In the third group of staphylococcal infections are included such conditions as primary and secondary cutaneous infections, wound infections, dental abscesses, mastitis, otitis, sinusitis, pharyngotonsillitis, enteritis, osteomyelitis and most urinary infections. Aside from considerations of the availability of other effective, intestinally absorbable, less toxic antibiotics and the desire to restrict the use of methicillin and similar drugs in the interest of minimizing staphylococcal resistance to them, the infections in this group demand less heroic therapy since they are unlikely to prove fatal if they remain uncomplicated. Many of the infections in this group require minimal or no antibacterial therapy, since they may subside spontaneously or after surgical drainage. Unlike the infections in the preceding two groups, most of them are "open infections," and their discharges are likely to cause greater dispersal of strains that acquire resistance. Also osteomyelitis frequently is a chronic infection, and prolonged therapy with one of the penicillinase-

resistant semisynthetic penicillins may enhance staphylococcal resistance to these agents.

I shall attempt to present, in the general order of choice, the agents used in this group of infections. It is obvious that use of vancomycin or combined therapy will rarely if ever be necessary in pharyngotonsillitis, dental abscesses and the like. Generally speaking, if the staphylococci resistant to penicillins G and V have been sensitive to it, erythromycin has been the agent of choice since it is orally absorbed and virtually nontoxic. With the availability of lincomycin, one has to choose between it and erythromycin, but the latter agent has the virtue of being relatively nontoxic and of having established its therapeutic efficacy over the last 15 years. Next, one can consider triacetyloleandomycin, which is also orally absorbed, since there is about a 70 per cent chance that erythromycin-resistant staphylococci may be sensitive to its action. However, like the propionyl ester of erythromycin, it is potentially hepatotoxic, especially if given for longer than 2 weeks. For this reason novobiocin may be preferred, but use of this drug is associated with a relatively high incidence of allergic dermatitis.

In the unlikely situation that erythromycin, lincomycin, triacetyloleandomycin or novobiocin cannot be used, then a penicillinase-resistant semisynthetic penicillin may be the drug of choice. When these drugs are not applicable, as in patients who have known allergy to penicillin, cephalothin may be tried. Kanamycin is considered before vancomycin since, although both are ototoxic, kanamycin is given intramuscularly whereas vancomycin must be given intravenously. Because of its propensity to depress the bone marrow, chloramphenicol is second to vancomycin in choice despite its virtue of being absorbed when given orally. It precedes consideration of ristocetin, which not only has a hematotoxic effect but also requires intravenous administration.

Before or after consideration of chloramphenicol and ristocetin, depending on one's fear of ill effects on the marrow as well as depending on the laboratory facilities available, one can consider combined antibiotic therapy as outlined previously. However, the need for such cumbersome therapy is rare in infections of this group. Excellent laboratory facilities are required for intelligent application of combined therapy.

Evaluation of combined therapy by serum bactericidal tests during treatment of certain conditions with agents empirically selected may be preferable to that based on pretreatment in vitro susceptibility tests with the use of various agents in combination. If one uses the latter method, one should check in vivo results with serum bactericidal tests to ascertain whether the effect predicted by the in vitro tests is being obtained.

Because of the effect of the tetracyclines on the body flora and of possible staphylococcal superinfection, use of these drugs in hospitalized patients is avoided. Streptomycin, to which staphylococci rapidly develop resistance, and both polymyxin B and colistin, which lack significant antistaphylococcal action, usually are not considered in the treatment of staphylococcal infections. Of the chemotherapeutic agents, nitrofurantoin (Furadantin), because blood concentrations of it are

minimal and fleeting, is used only in certain mild urinary infections. Sulfonamides, primarily because of the problem of resistance, have no major role in managing serious staphylococcal infections.

While one is desirous of relying on in vitro susceptibility tests in the management of staphylococcal infections, time does not always allow such investigation. When staphylococcal infections demand treatment before such data are available, one gives a drug to which the staphylococci are most likely to be sensitive. A penicillinase-resistant semisynthetic penicillin, cephalothin, kanamycin, vancomycin, lincomycin or chloramphenicol may be selected in about that order of choice, and when results of susceptibility tests are known, one may substitute an agent that is more effective, less toxic, or both. In instances of suspected staphylococcal bacterial endocarditis, of course, one would not consider the use of a bacteriostatic agent such as chloramphenicol.

UNTOWARD EFFECTS

Among potential untoward effects, allergy is the chief difficulty encountered with the use of the penicillins. It is estimated that allergy to the penicillins is present in 3 to 5 per cent of the general population, and in up to 10 per cent of subjects who previously have been treated with the drugs. Cross-allergenicity among the natural penicillins and the semisynthetic penicillins apparently reflects the 6-APA nucleus which they have in common. Various methods employed in attempts to identify subjects allergic to the penicillins include skin testing with the drugs as well as with the derivative penicilloyl-polylysine,[40] conjunctival testing, serum hemagglutination tests,[53] indirect basophilic degranulation tests[42] and passive transfer tests; none of these, however, is infallible. It is theorized that catabolic products of the penicillins, such as penicilloyl compounds, may unite with body protein and be responsible for most of these allergic reactions. Oral administration of a penicillin is least likely to induce hypersensitization, topical application is most likely, and parenteral administration is intermediate in this regard. Persons having a so-called allergic diathesis, with a history of such conditions as asthma, eczema or hayfever, are more likely to demonstrate hypersensitivity, particularly anaphylaxis, on use of the penicillins. The problem of penicillin sensitization is complicated further by sources of inadvertent acceptance of the drug, such as milk, fowl and viral vaccines.

Desensitization may be helpful in avoiding further reactions to the penicillins. Such substances as antihistaminics, penicillinase and corticosteroids may help combat some reactions of hypersensitivity to the penicillins. However, penicillinase also may cause allergic reactions, and the enzyme likely would not be helpful in cases wherein a penicillinase-resistant drug is causative. Although corticosteroids are of use in allergic states, the presence of infection sometimes makes it hazardous to use such agents.

It is common experience that various skin reactions, including contact dermatitis, angioneurotic edema, glossitis, stomatitis, drug

fever, serum sickness, asthma and anaphylaxis, may complicate the use of the penicillins. The incidence of fatality in cases of anaphylaxis is estimated to be nearly 10 per cent. More unusual reactions include purpura, pericarditis, toxic psychoses and hematemesis due to an urticaria-like reaction of the gastric mucosa. Diffuse vasculitis may be a rare manifestation of penicillin hypersensitivity. Gastrointestinal irritation, including diarrhea, may occur after the use of an orally administered penicillin, but such irritations are seldom severe enough to require discontinuation of therapy. Pain on intramuscular injection of the semisynthetic penicillins is more likely on use of ampicillin and nafcillin. Sterile abscesses rarely may occur at the site of intramuscular injection of the penicillins.

In patients whose intake of sodium should be restricted, such as those with heart failure or renal dysfunction, who are receiving one of the semisynthetic penicillins, the increased intake of sodium must be considered. As an example of this, one should recall that each 4 gm. of methicillin supplies 230 mg. (10 mEq.) of ionic sodium.

Granulopenia and anemia have occurred after administration of methicillin.[33] Oxacillin has caused transient leukopenia. Some of the newer penicillins have been accused of other forms of hematotoxicity on occasion, but these contentions are more difficult to establish.

The penicillins, when given in large amounts, may cause cortical irritation (including convulsions), especially in patients having decreased renal function. Chronic brain damage may result. Since the penicillins in addition have precipitated acute psychosis and since anaphylactic reactions also have resulted in chronic brain damage,[5] perhaps one should be more aware of the potential neurotoxicity of these drugs.

Whether methicillin has significant nephrotoxic effects is not certain at this writing, but this appears likely.[8]

During therapy with ampicillin, oxacillin, and cloxacillin, the serum glutamic oxaloacetic transaminase activity may be increased, but the exact significance of this is not clear. Oxacillin has been accused of causing hepatic toxicity,[9] including cholestatic hepatitis.[49]

Phenethicillin, oxacillin, cloxacillin and nafcillin are not well absorbed after oral administration unless the stomach is otherwise empty. Food interferes with the absorption of these drugs, and consequently the decreased levels in serum might be insufficient to eradicate an infection.

Use of the penicillins may depress the coccal members of the body flora and encourage the development of bacteremia, urinary infection, pneumonia, and other infections caused by overgrowth of resistant organisms such as gram-negative bacilli and Candida. Periodic examination of the sputum and stools may allow detection of changes in the body flora in time to avert clinical superinfection. As an example of this complication, in series of patients treated with methicillin, as many as a third have experienced superinfections due to gram-negative bacilli; fatal bacteremia due to gram-negative bacilli has occurred. Ampicillin-

induced superinfections are most frequently due to Pseudomonas and Klebsiella-Aerobacter organisms.[52]

As aforementioned, strains of S. aureus isolated from clinical material in British hospitals have demonstrated an increasing incidence of resistance to methicillin.[6, 14, 48] These strains may show a corresponding increase in resistance to other commercially available penicillinase-resistant semisynthetic penicillins.[2, 38] The presumption is that when these drugs have been employed in a given environment for a period of time, strains of staphylococci will demonstrate increasing resistance to their action, as has occurred in Britain. This ominous possibility should be sufficient to militate against indiscriminate use of these drugs. It appears that coagulase-negative strains of staphylococci are even more prone to emerge as being resistant to methicillin and allied drugs than are coagulase-positive strains.

The serum concentrations of all the penicillins, both natural and semisynthetic, may be increased on conjoint administration of probenecid (Benemid),[7] which blocks the renal tubular excretion of these antibiotics. However, some patients are unable to tolerate probenecid because of gastrointestinal irritation. Also, some practitioners do not favor use of probenecid because its side effects may be confused with those of the penicillins or with manifestations of the infection being treated. Such side effects of probenecid include dermal reactions, anaphylaxis, fever, chills, anemia and possibly the nephrotic syndrome.[46] Of course, concomitant administration of probenecid in infections of the urinary tract would not be advisable, since decreased urinary concentration of the antibiotic would be likely.

CONCLUSIONS

The semisynthetic phenethicillin and penicillin V are used more or less interchangeably. Of the penicillinase-resistant drugs, oxacillin, cloxacillin and nafcillin are more active by weight than methicillin and can be given orally as well as parenterally. Serum levels of cloxacillin may be twice as high as those of oxacillin. Nafcillin is sometimes preferred because of its more persistent serum and tissue levels. Ampicillin has been effective in serious infections due to gram-negative bacilli, including influenzal meningitis and bacteremia due to E. coli.

Long-term evaluation is required in order to assess the comparative advantages of new antibiotics and the continued value of older ones. This is so because the benefits as well as the untoward effects of a drug may not become known until several years have elapsed after its clinical availability. Their untoward effects, which may become apparent on further observation, may influence considerations regarding the ultimate clinical application of the individual semisynthetic penicillins.

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New Antimicrobics for the Treatment of Infections Caused by Gram-Negative Bacilli

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Serious infections caused by gram-negative bacilli continue to wax in frequency of occurrence.[23, 24, 44, 56, 67, 82, 88] This trend is attributable, in large part, to the spate of noncurative therapies for noninfectious illnesses that now preserve many persons for eventual infection.[56] Gram-negative bacilli are frequently involved because these bacteria are (1) in plentiful supply—in the lower enteric tract and in the environment external to the body; (2) capable of invading in persons already diseased; and (3) often resistant to many kinds of antimicrobial agents.

Seven agents that have been introduced since 1960 will be discussed. These are colistin, ampicillin, methacycline, cephalothin, nalidixic acid, gentamicin and cephaloridine; some attributes of these drugs are presented in Tables 1 and 2. In addition, pertinent aspects of clinical pharmacology are summarized in Tables 3 and 4.

Notable among the pharmacologic data are those dealing with excretion of the tabulated antimicrobics. Some general discussion is in order because these drugs (1) have renal excretion as a major egress from the body; (2) are often indicated in the treatment of infections caused by gram-negative bacilli, frequently in the setting of urinary tract infections; and (3) in four instances, bear significant potential for toxic injury to the patient. One consequence of these factors is the frequent and perplexing problem of safe, effective use of essential, potentially toxic antimicrobics in persons with renal insufficiency. The aim can be stated clearly: enough of the antimicrobial agent must be given to replenish the quantity of drug eliminated, so that therapeutic

(Text continued on page 1132.)

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Table 1. *Attributes of Newer Antimicrobics Effective in Treatment of Infections Caused by Gram-Negative Bacilli*

AGENT (TRADE NAME AND MANUFACTURER)	YEAR INTRODUCED	SOURCE	CHEMICAL VARIETY	MOLECULAR WEIGHT	STABILITY
Colistin Coly-Mycin, Warner-Chilcott	1960	Bacillus polymyxa var. garyphalus	Peptide	968.3*	Stable in aqueous solution at pH ≤ 6.0; stability ↓ as pH ↑
Ampicillin Polycillin, Bristol Penbritin, Ayerst Omnicillin, Wyeth	1961	Semisynthetic	Peptide	367.4†	Most resistant to degradation by acid of penicillins in use; degraded by penicillinase
Methacycline Rondomycin, Pfizer	1961	Semisynthetic	Tetracycline group	440.4*	Stable in aqueous solution for 3 to 5 days at pH 7.0, 4° C.
Cephalothin Keflin, Lilly	1962	Semisynthetic	Peptide	396.4†	Stable in aqueous solution over pH range 5–8; not affected by penicillinase
Nalidixic Acid Neg-Gram, Winthrop	1962	Synthetic	Naphthiridine derivative	232.2†	Aqueous solution can be autoclaved
Gentamicin Garymycin, Schering	1963	Micromonospora purpurea	Aminoglycosyl	407*	Aqueous solutions of pH 5.5 to 6.0 can be autoclaved for 30 minutes
Cephaloridine Keflordin, Lilly Ceporin, Glaxo	1964	Semisynthetic	Peptide	415.5‡	Aqueous solutions at pH 7.0, 20° C., lose < 5% of activity per day

*As the free base

†As the free acid

‡As the betaine

Table 2. *Antimicrobic Activity and Cost of Newer Agents Effective in Treatment of Infections Caused by Gram-Negative Bacilli*

AGENT	MECHANISM OF ACTION	PRINCIPAL GRAM-NEGATIVE BACILLI		COST TO PHARMACIST (DRUG TOPICS RED BOOK, NEW YORK, TOPICS PUBLISHING CO., 1967).
		SUSCEPTIBLE	RESISTANT	
Colistin	Bactericidal Surfactant on cell membrane	Pseudomonas sp. Escherichia coli	Proteus sp. Providencia sp.	Oral: $0.43 per 5 ml. suspension (25 mg.) Injectable: $5.95 per vial (150 mg.)
Ampicillin	Bactericidal Interference with cell wall synthesis	Hemophilus influenzae	Pseudomonas sp. Indole + Proteus sp. Providencia sp.	Oral: $0.18 per 5 ml. suspension (125 mg.) $0.30 per 5 ml. suspension (250 mg.) $0.29 per capsule (250 mg.) $0.52 per capsule (500 mg.) Injectable: $1.74 per vial (250 mg.) $2.28 per vial (500 mg.) $3.36 per vial (1000 mg.)
Methacycline	Bacteriostatic Interference with protein synthesis	Rickettsia sp. Brucella sp. Bedsonia sp.	Proteus sp. Providencia sp. Pseudomonas sp. Tribe: Klebsielleae Salmonelleae	Oral: $0.14 per 5 ml. syrup (75 mg.) $0.19 per capsule (150 mg.) $0.34 per capsule (300 mg.) Injectable: Not available
Cephalothin	Bactericidal Interference with cell wall synthesis	Klebsiella sp.	Indole + Proteus sp. Pseudomonas sp. Providencia sp.	Oral: None Injectable: $3.24 per vial (1000 mg.)
Nalidixic Acid	Bactericidal Blockage of synthesis of DNA	Family: Enterobacteriaceae	Pseudomonas sp.	Oral: $0.09 per tablet (250 mg.) $0.16 per tablet (500 mg.) Injectable: Not available
Gentamicin	Bactericidal Surfactant on cell membrane Interaction with RNA → faulty transcription	Pseudomonas sp. Tribes: Escherichieae Salmonelleae Proteeae Klebsielleae	Some Enterobacter sp.	Oral: Not available Topical: $1.56 per tube cream (15 gm.) $1.56 per tube ointment (15 gm.) Injectable: Not available
Cephaloridine	Bactericidal Interference with cell wall synthesis	Klebsiella sp.	Indole + Proteus sp. Providencia sp. Pseudomonas sp.	Not yet available

Table 3. *Pharmacologic Properties of Newer Antimicrobics Effective in Treatment of Infections Caused by Gram-Negative Bacilli*

	ABSORPTION		DISTRIBUTION		EXCRETION			
AGENT	GUT	PARENTERAL	EXTRACELLULAR	CSF	FATE	ROUTE	T½ BLOOD	TOXICITY
Colistin	0 to +	I.M.	√	0	Mostly excreted unchanged by the kidneys	40 to 80% in urine	1.6 to 2.7 hours	Neuro- and nephrotoxicity
Ampicillin	++	I.M. I.V.	√	+*	Excreted unchanged by liver and kidneys	55 to 70% in urine	1.3 to 1.6 hours	None (hypersensitivity)
Methacycline	++	Not given	√	+*	Bound to osseous tissues, thyroid; excreted unchanged by liver and kidneys	60% in urine	14.3 hours	Gastrointestinal upset; hepatotoxicity.
Cephalothin	0	I.M. I.V.	√	+*	Hepatic deacetylation (≅ 30%); excreted unchanged	60 to 90% in urine	0.5 to 0.85 hours	None (hypersensitivity
Nalidixic Acid	++++	I.V.	0†	0	About 90% metabolized	80 to 100% in urine	1.5 to 1.7 hours‡	Neurotoxicity
Gentamicin	0 to +	I.M. I.V.	√	+*	Excreted unchanged	86 to 100% in urine	2.3 hours	Vestibulotoxic and nephrotoxic
Cephaloridine	0 to +	I.M. I.V.	√	+*	Excreted unchanged	70% in urine	1.5 hours	None (hypersensitivity)

*Penetration when there is meningeal inflammation

†Unmeasurable to very low in plasma after oral dosage; quite transiently present after I.V. injection—antimicrobially active drug

‡By spectrofluorometric measurement, i.e., mostly inactive drug

Table 4. *Dosage of Antimicrobial Agents According to Excretory Capacity*

Agent (route)	Dose, in mg. per kg. body weight, when creatinine clearance is: Normal or ≥ 80% of normal	<80% to >30% of normal	<25% of normal; BUN = 100 mg. per 100 ml.	Dose, in mg. per kg. body weight, in presence of anuria	Effect of dialysis
Colistin (parenteral)	2.5 to 5.0 mg. each day	1st day: 2.5 mg. Daily thereafter: 1.0 to 2.0 mg.	1st day: 2.5 mg. Every 48 to 72 hrs.: 1.0 to 2.0 mg.	1st day: 2.5 mg. Every 5 to 7 days: 1.0 mg.	Not appreciable
Ampicillin (parenteral)	50 to 200 mg. each day	50 to 200 mg. each day	50 to 200 mg. each day	1st day: 50 to 200 mg. Daily thereafter: 25 to 100 mg.	Not appreciable
Methacycline (oral)	8 to 10 mg. each day	Do not use	Do not use		Do not use
Cephalothin (parenteral)	40 to 200 mg. each day	40 to 200 mg. each day	40 to 150 mg. each day	1st day: 40 to 200 mg. Daily thereafter: 25 to 75 mg.	Not known
Nalidixic acid (oral)	25 to 50 mg. each day	10 to 25 mg. each day	Do not use	Do not use	
Gentamicin (parenteral)	1.5 to 2.0 mg. each day	1st day: 1.5 mg. Daily thereafter: 0.7 to 1.5 mg.	1st day: 1.5 mg. Every 3 to 5 days: 0.7 to 1.5 mg.	1st day: 1.5 mg. Every 7 to 9 days: 0.5 to 0.7 mg.	Not known
Cephaloridine (parenteral)	20 to 80 mg. each day	1st day: 20 to 80 mg. Daily thereafter: 10 to 25 mg.	1st day: 20 to 80 mg. Daily thereafter: 5 to 10 mg.	1st day: 20 to 80 mg. Daily thereafter: 1 to 5 mg.	Significant removal; give 10 to 25 mg. per kg. after dialysis

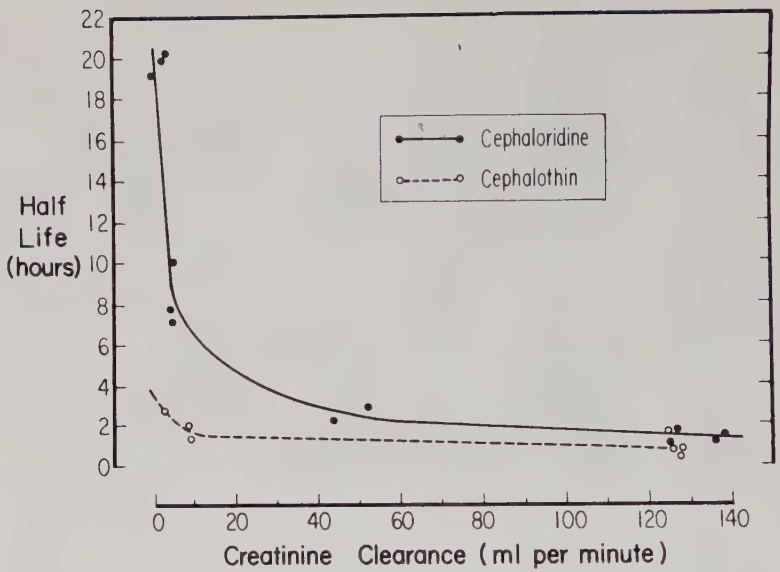

Figure 1. The halflife in the serum of cephalothin and cephaloridine (after single injections of 0.5 gm. intramuscularly) is related to the creatinine clearance in this set of curves. (Reproduced from Figure 2 of Kunin and Atuk[47] by permission of the New England Journal of Medicine.)

concentrations are maintained in the blood and other body fluids. Such rational conduct of therapy requires knowledge of the blood concentration of the antimicrobic that is current. The bioassay methods now available generally require 48 hours for completion—the data are too remote in time to be of aid in therapy. Consequently, the physician must guess at the efficiency of renal clearance of antimicrobial agent, interpolating from multiple parameters of renal function. Urea clearance, blood urea nitrogen, creatinine, volume of output and formed elements of the urine are most helpful and must be observed daily, or every other day, especially when therapy with potentially nephrotoxic agents is necessary in the face of renal failure. Other organs may signal toxic injury indicating need for reduction in dose, e.g., neurotoxicity evidenced by confusion or ataxia.

A sophisticated approach, yet developing, may be most useful. Plotting the halflife of antimicrobic in the serum against the creatinine clearance (as in Fig. 1) establishes a relationship possibly of predictive value. For a given reduction in creatinine clearance, a corresponding increment in drug halflife can be adduced. Appropriate reduction from the normal dose should be inversely proportional to the prolongation of drug halflife. However, a broad informational base is not yet available; observations of drug halflife versus creatinine clearance are needed in many patients, relating to several antimicrobial agents. Moreover, there is, as yet, little clinical experience with this approach. In practice, modification of dosage of antimicrobial agents in patients with renal failure remains quite empiric.[46a] Guidelines are given in Table 4.

Except for methacycline, each of the agents under discussion will, in some circumstances, have to be given by parenteral administration. Intramuscular injection is frequently employed. However, there are circumstances when intravenous injection is preferable: (1) when pain from repetitive intramuscular injection is severe and cannot be ameliorated by admixture of a local anesthetic; (2) if there is shock, for absorption of intramuscularly deposited drugs will then be erratic and inefficient; (3) in patients with a bleeding tendency, intramuscular injection may provoke hematoma formation. Intravenous administration can be either intermittent on continuous. Intermittent injection will produce high blood concentrations for short periods of time. The author's preference for continuous intravenous infusion of antimicrobics arises from (1) less irritation of veins, that is, less thrombophlebitis, than is caused by the more concentrated solutions used for intermittent injection; (2) less demand on personnel; and (3) rational therapeutics —a sustained, moderate gradient favors continuous passage of antimicrobic from blood to site of infection, while the higher gradient of intermittent intravenous injection is only fleetingly operative.

COLISTIN

Colistin is identical with polymyxin E.[86] Its discovery, then, must actually be dated to 1947 when resolution of the polymyxins was accomplished.[11] At that time, polymyxin B was judged preferable for therapy However, polymyxin E eventually succeeded to therapeutic use under the new name colistin after rediscovery in 1952.[45]

CLINICAL PHARMACOLOGY. In addition to the data of Table 3, it should be noted that there is significant absorption of colistin from the gut of infants.

The dynamics of antimicrobially active colistin in blood and urine are complex. Not only are absorption, distribution, renal excretion and nonrenal disposition involved, but so also are the rate and extent of hydrolysis of the relatively inactive sulfomethyl derivative that is used for injection to release fully active colistin base. Two to three hours after intramuscular injection,[52, 57] blood concentration will be maximal at 5 to 10 μg. per ml.—assuming normal renal function and ordinary dosage (2.5 to 5.0 mg. per kg. body weight per day given in two or three equal portions). Most of the colistin is gone from the blood by 6 hours after injection. There is no tubular reabsorption and the concentration of active colistin in the urine is 2 to 20 times that in the blood.

PREPARATIONS AND DOSAGE. For oral administration, colistin sulfate is marketed as a dry powder. After suspension in water, the usual dose is 3 to 5 mg. per kg. body weight per day, given in three equal portions.

Colistin for intramuscular injection is packaged as the sodium salt of the sulfomethyl derivative, with admixed dibucaine hydrochloride. Because of the dibucaine (8 mg. per 150 mg. colistin—free base equivalent), this preparation cannot be injected into the subarachnoid space.

Intravenous injection is not recommended. As noted above, the intramuscular dose varies from 2.5 to 5.0 mg. per kg. body weight per day given in two or three equal portions. For effectiveness against Pseudomonas sp. the higher dose is necessary.[57]

ADVERSE REACTIONS. Oral administration has no direct adverse effect on bowel function. However, abnormal preponderance of Proteus sp. may come to pass as elements of the normal enteric bacterial flora are suppressed. Absorption of colistin from the gastrointestinal tract may be sufficient in infants to cause renal injury.

Neurotoxicity and nephrotoxicity, the major toxic hazards, are most commonly engendered by parenteral administration of colistin. Circumoral, lingual and acral paresthesias, with or without pruritus, head the list of manifestations of neurotoxicity. Paresthesias often disappear without change in dosage. Vertigo, dizziness, ataxia, visual disturbances, confusion, dysphonia and apnea[63, 89] are of more serious portent and require reduction of the dose or temporary cessation of therapy.

Injury to renal tubular cells can lead to cylindruria, azotemia, oliguria and acute renal failure.[22] The appearance of casts does not obligate change in dosage but indicates need for close surveillance. With azotemia the dose must be reduced (see Table 4); oliguria forces drastic reduction or termination of colistin treatment.

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. Infections caused by Pseudomonas sp. are the major indication for the therapeutic use of colistin.[31, 54] The susceptibility in vitro of isolates of E. coli has its counterpart in favorable effect from treatment with colistin on infections caused by E. coli.[31, 54] The experience is smaller, but similar, with Klebsiella sp. and with Enterobacter sp. While isolates of Salmonella sp., Shigella sp., Hemophilus sp., Bordetella sp., and other less commonly encountered gram-negative bacilli may be susceptible to colistin by in vitro testing, there is no clinical experience confirmatory of good effect. Proteus sp. and Providencia sp. are notable among gram-negative bacteria for virtually uniform resistance to colistin.

Colistin is not the agent of first choice in treatment of infections caused by non-Pseudomonas gram-negative bacilli. Other, better tolerated agents are usually equally or more effective. However, in those infections caused by non-Pseudomonas gram-negative bacilli that are susceptible to colistin but resistant to safer agents, colistin can be used.

When kidney function is reduced, the dose of colistin must be decreased to compensate for the diminution in renal excretory capacity. The rationale has been discussed, and guidelines are given in Table 4.

There is complete cross susceptibility-resistance of bacteria when colistin and polymyxin B are compared. The author's preference for polymyxin B has these bases:

1. To the same degree, both antimicrobic potency and toxic liability are less with colistin than with polymyxin B. That is, for comparable antibacterial potency, identical toxic hazard is risked.[58]

2. Pain referred to the site of intramuscular injection of polymyxin B (available only as the sulfate) can be mitigated by solution of the drug

in 2 per cent procaine. In some patients, however, pain becomes troublesome 4 to 6 hours after injection, when the procaine is dissipated; continuous intravenous injection can then be used. Injected with dibucaine and in a chemical form that masks the cationic detergent character of the compound, colistin (as the sulfomethyl derivative for injection) usually does not cause pain on intramuscular injection; however, it cannot be given intravenously.

3. Because polymyxin B is injected as the sulfate, no hydrolysis is required to release active antimicrobic. Moreover, since polymyxin B is compounded as a simple salt for injection it can be given intravenously, a matter of importance in patients who are in shock; intrathecally, essential for effective treatment of meningitis with the polymyxins; or intraocularly in treatment of eye infections.

4. Polymyxin B is less costly than colistin.

AMPICILLIN

Ampicillin (α-aminobenzylpenicillin) is the acylation product of 6-aminopenicillanic acid and D-α-aminophenylacetic acid. Three attributes of this agent are notable: (1) a resistance to degradation by acid that is unsurpassed among penicillins available for therapy;[18] (2) susceptibility to penicillinase of a degree comparable to that of benzylpenicillin;[3] (3) a shifted antibacterial spectrum as compared with penicillin G—more active against some kinds of gram-negative bacteria, such as Hemophilus influenzae, but less potent against some kinds of gram-positive bacteria, for example, one half to one fourth as active against Group A Streptococcus pyogenes.[42, 68] Hetacillin, a semisynthetic congener of ampicillin, does not differ significantly from the parent compound in antimicrobial activity or potency.[4, 61]

CLINICAL PHARMACOLOGY. The data of Table 3 merit some expansion. It is noteworthy that absorption of ampicillin from the gastrointestinal tract is adequate for therapy, but is not complete (see Fig. 2). Destruction in the gut probably does not account entirely for the sevenfold greater concentration of ampicillin in the blood after intramuscular injection as compared with an equal dose given orally.[70] The regions of the intestine where bacterial inactivation is most likely to occur are distal to the duodenum where absorption is maximal. Enterohepatic cycling—hepatic removal of ampicillin from the blood, excretion in the bile, reabsorption from the intestine—is operative regardless of route of administration. However, it may be significant that oral administration obligates hepatic access to ampicillin prior to general distribution in the body. After oral administration, only 20 to 40 per cent of the drug appears in the urine during the next day,[42, 43] while 55 to 70 per cent of injected doses are accounted for in the urine.[20]

The tubular secretory component of renal excretion can be antagonized by probenecid.[20] Depending on the rate of urine formation and on whether probenecid was given, from 100 to 1500 μg. of ampicillin per ml. of urine results in the 6 hours following parenteral injection of a

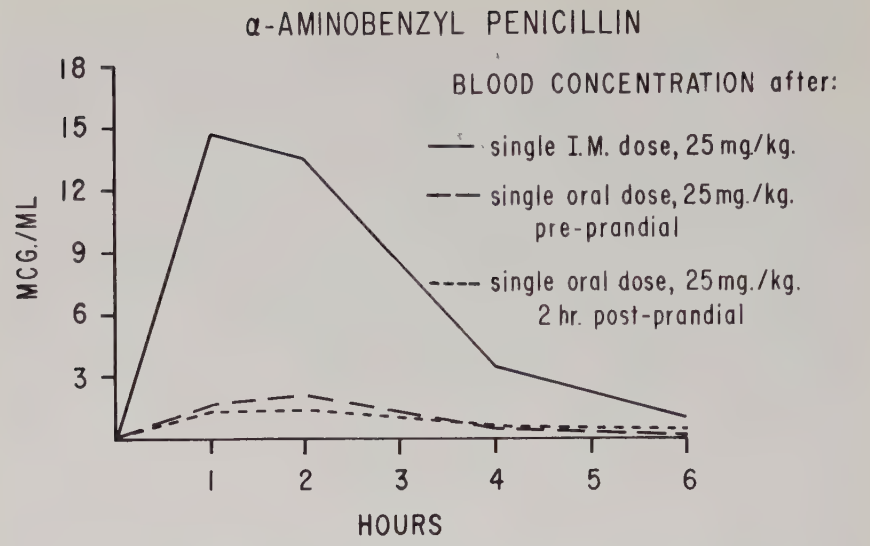

Figure 2. There was detectable, but slight, influence from ingestion of food on the absorption of ampicillin. However, absorption from the gut is meager, yielding about one seventh the concentrations in the blood that follow intramuscular injection of equal doses. (Redrawn from Figures 1 and 2 of Ross et al.[70] by permission of the Journal of the American Medical Association.)

single 0.5 gm. dose in adults.[20] Hepatic removal and excretion of ampicillin in the bile is probably augmented when renal tubular secretion is interfered with by probenecid, for total urinary excretion is decreased.

PREPARATION AND DOSAGE. Ampicillin for oral administration is supplied as the trihydrate in powder from (when suspended in water, each 5 ml. contains 125 mg.) and as capsules (250 mg. each).

The dose for children is 50 to 100 mg. per kg. body weight per day given in four equal portions at 6-hour intervals. Dosage in adults varies from 1 to 8 gm. per day, also split into four equal portions taken at 6-hour intervals. The larger doses, in both children and adults, may cause diarrhea. Generally, this is not severe and can be controlled with paregoric or codeine.

For injection, the dry sodium salt of ampicillin is marketed in vials containing 250 mg., 500 mg. and 1000 mg. Solution of the contents of a vial in 1.2 to 2.2 ml. of water for injection permits removal of the ampicillin in a volume suitable for intramuscular injection. When the total dose exceeds 4 gm. per day, or when the pain from repetitive intramuscular injection is a serious complaint, continuous intravenous injection is preferable. Solutions of sodium ampicillin in isotonic sodium chloride (2 to 30 mg. per ml.) will lose less than 10 per cent of biologic activity in 8 hours at room temperature; when 5 per cent glucose solution is the vehicle, 4 hours at room temperature will produce a comparable loss of activity.

Parenteral dosage in children and adults ranges from 25 to 300 mg. per kg. body weight per day. Bacterial meningitis and endocarditis have

been indications for maximal dosage.[53, 62] The lower doses can be given in four equal portions by intramuscular injection every 6 hours; continuous intravenous injection is effective and more humane when larger doses are required.

With renal failure, there may be a decrease in excretion of ampicillin that is not compensated by augmented biliary excretion. The phenomenon of seizures precipitated by administration of large doses of penicillin G in patients who have renal insufficiency[60] has not been associated with ampicillin. However, when there is renal failure, some modification in dosage is advisable (see Table 4).

ADVERSE REACTIONS. The major adverse reaction with ampicillin is that encountered with all penicillins—hypersensitivity. Skin rashes, pruritus and urticaria have been described. Experience to date indicates that ampicillin is neither more nor less prone to engender hypersensitivity than other penicillins. When a clinical reaction of hypersensitivity has been provoked by another penicillin, ampicillin should not be used, for it can trigger recurrence.[77]

Nausea, vomiting and diarrhea may occur with oral administration. Pain after intramuscular injection is another annoying effect that is not prohibitory to therapy.

Elevation of serum glutamic oxaloacetic transaminase has been observed, especially when high doses have been given. Such elevations have been temporary and may reflect the burden large doses place on the liver in achieving biliary excretion.

The consequences of exposure of the immature (in and extra utero) infant and newborn child have not been fully assessed.

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. Discussion of the utility of ampicillin in treatment of infections caused by enterococcal group bacteria is outside the scope of this paper, but it should be noted that infection caused by this group of bacteria appears to be a special indication for treatment with ampicillin.[10, 68]

The results of treatment of meningitis caused by Hemophilus influenzae with ampicillin given alone in doses of 150 to 400 mg. per kg. body weight per day by intravenous injection have been gratifying.[6, 27, 53] While there is no proof that 400 mg. per kg. is more effective than 150 mg. per kg., it is clear that ampicillin used alone is at least as effective as the older, multiagent regimens.[6, 27, 53] However, it has not been shown that ampicillin used alone is more effective than benzylpenicillin used alone *in comparable dosage* for treatment of meningitis caused by H. influenzae. Differences in the susceptibility of clinical isolates of H. influenzae to ampicillin and to benzylpenicillin are so small[6, 36, 74] as to augur no difference in the outcome of treatment with either penicillin. The early disappointment with penicillin G in therapy for influenzal meningitis is not relevant, for the doses given were minuscule in comparison with 150 mg. per kg. body weight—total daily dosage was 23 to 315 mg., or about 2 to 20 mg. per kg. per day.[19, 79, 90] It is remarkable that the recovery rate was 58 per cent. It may be that the clinical experience of inadvertent cure of patients with meningitis caused by H. influenzae with penicillin G[35] should be heeded.

Escherichia coli. By in vitro testing about 80 per cent of clinical isolates of Escherichia coli are inhibited from growth by ampicillin, as they are by a large variety of antimicrobial agents.[2, 68] Indeed, when testing is carried out carefully, ampicillin is actually not significantly more potent than benzylpenicillin in anti-E. coli effect.[34] There is on record clinical experience which asserts to the effectiveness of ampicillin in treatment of urinary tract infections caused by E. coli.[2, 10] Benzylpenicillin and phenoxymethylpenicillin are also effective.[76] These penicillins are effective because (1) high concentrations are achieved in the urine; (2) urinary tract infections are commonly infranephric; and (3) the usual cause is nonhospital E. coli with multiagent susceptibility. Both benzylpenicillin and phenoxymethylpenicillin are less costly to the patient than is ampicillin, and the latter agent is both reliably and well absorbed after oral administration.

When there is more serious infection by E. coli, such as bacteremia, a case can be made for use of ampicillin only if it has been ascertained that the E. coli involved is susceptible to ampicillin—that is, killed in vitro by 25 μg. or less per ml. Until this determination is made, an agent with higher probability of effectiveness, such as polymyxin B, should be used. Large doses of ampicillin are necessary—100 to 200 mg. per kg. body weight (8 to 20 gm. per day). It is of more than passing interest that large doses of penicillin G (40 to 60 megaunits, equivalent to 25 to 38 gm. per day) may be effective therapy for serious infections caused by E. coli.[83]

In short, for the common, lower (nonrenal) urinary tract infections caused by extrahospital kinds of E. coli, ampicillin will be effective in low to moderate oral dosage. However, comparable effectiveness and lower cost recommends use of penicillin V in this situation. Serious infections, particularly bacteremia with E. coli, are best treated, at least initially, with polymyxin B.

Proteus sp. Clinical isolates of P. mirabilis are usually susceptible to ampicillin, as they are to benzylpenicillin. However, the degree of susceptibility is somewhat greater to ampicillin.[5] Yet, for renal or extraurinary tract infections, high-dosage therapy is necessary with either kind of penicillin (8 to 25 gm. per day). For reasons of comparable potency and lesser cost, penicillin G remains preferable in such situations. None of the penicillins is usefully active against the indole-positive Proteus sp. and Providencia sp.

Salmonella sp. Several attributes recommend consideration of ampicillin for treatment of salmonellosis: safety; ease of administration; high probability of effectiveness according to in vitro testing;[40] and excretion by the liver with actual concentration in the bile.[78]

Typhoid fever has been an indication for antimicrobial therapy, as much because of the gravity of the disease as because of the documented effectiveness of chloramphenicol. Ampicillin is clearly not as effective as chloramphenicol for treatment of acute typhoid fever.[16, 41, 73] It was hoped that a consequence of hepatobiliary concentration of ampicillin would be the prevention of convalescent carriers; again,

ampicillin has not been successful.[41, 64] Regarding the third facet of typhoid, the resolution of established, true carriers—persons who continue to shed Salmonella typhi in the feces one year after the acute illness—there is disagreement. One author reported cure of seven of eight typhoid carriers after 3 months' treatment with ampicillin.[15] Several other reports,[14, 55, 81] dealing with a total of 16 true carriers of S. typhi, tell of failure of clearing in 13 patients. McFadzean's report[55] is especially pertinent since there was failure of cure of eight carriers (of eight treated), although all eight had cholecystectomy 2 to 16 years previously; ampicillin was given for 6 months along with probenecid.

Nontyphoidal salmonellosis appears to be of increasingly frequent occurrence. In the common gastrointestinal form of the disease, antimicrobial therapy is not indicated.[51, 72] Bacteremia, extraenteric involvement, infection in hypersusceptible persons and, possibly, infection caused by the more invasive species of Group C, such as S. cholerasuis, are the bases for antimicrobic treatment. Chloramphenicol has not been entirely satisfactory; while immediate response is usually good, relapse may occur when chloramphenicol is discontinued, and convalescent carriers are not prevented. Ampicillin has been no more satisfactory in regard to both acute disease and carriers.[29, 41, 62, 64, 71] Ampicillin has not only failed to reduce the frequency of occurrence of convalescent carriers of nontyphoidal Salmonella sp., but it has also been ineffective in treatment of chronic carriers.[14, 41, 62, 64]

Ampicillin appears to be effective therapy for bacillary dysentery.[32, 70]

METHACYCLINE

When the nonchelating regions of the tetracycline molecule are manipulated, pharmacologic properties are most drastically affected. There may also be quantitative effect on antimicrobial potency, but there is no significant qualitative change. Methacycline (6-methylenoxytetracycline) is the most recently introduced of such semisynthetic congeners of tetracycline.[9]

CLINICAL PHARMACOLOGY. Methacycline is probably not as well absorbed after oral administration as some other tetracyclines.[46] Higher concentrations and persistence in the blood are consequences of delayed renal excretion and limited volume of distribution—both follow on more extensive binding to serum proteins. Other aspects of clinical pharmacology are given in Table 3.

PREPARATIONS AND DOSAGE. Methacycline is available only in forms for oral administration. Capsules contain either 150 mg. or 300 mg. of methacycline hydrochloride: the usual adult dose is 600 mg. per day given in two or more equal portions.

A syrup containing 75 mg. methacycline hydrochloride per 5 ml. is available. The usual pediatric dose is 10 mg. per kg. body weight given in three equal portions.

ADVERSE REACTIONS. None are attested by long clinical experience, but in general they appear to follow in the pattern of earlier tetracycline

drugs. Thus, the staining of osseous structures occurs. Allergy is uncommon; phototoxicity has not been associated with administration of methacycline. The hazard of hepatotoxicity is probably greater with a slowly excreted tetracycline derivative, such as methacycline, than it is with more rapidly eliminated tetracyclines. For this reason, when there is reduced renal function and a tetracycline is to be used, one of the original congeners is preferable.

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. Methacycline does not differ from other tetracyclines in antimicrobial spectrum, and so has no unique therapeutic indications. There is little reported clinical experience with methacycline, but infections caused by Bedsonia sp., Rickettsia sp. and Brucella sp. should respond to therapy with this agent.

Over the years, there has been a decline in the therapeutic efficacy of the tetracyclines as resistance has become increasingly common with many kinds of bacteria. Thus, infections caused by Escherichia sp. are better treated with other agents, as are infections caused by other genera of the family Enterobacteriaceae. Pseudomonas sp. remain beyond the reach of tetracyclines, methacycline included.

CEPHALOTHIN

Cephalothin results from acylation of 7-aminocephalosporanic acid with thiophene-2-acetyl chloride. It is the first derivative of 7-aminocephalosporanic acid to attain therapeutic use; as such, it represents but the first fruit of efforts that commenced in 1945 with Brotzu's finding of antibacterial activity in association with a Cephalosporium sp. isolated from rocks in the Mediterranean locale of the city of Cagliari's sewage outfall.[21, 28]

CLINICAL PHARMACOLOGY. Serum concentrations, maximal about one half hour after intramuscular injection (see Fig. 3), are about 10 μg. per ml. after a dose of 0.50 gm. and double with twice that dose.[8] Significantly higher serum concentrations result from identical doses given to premature and newborn infants[75] and to persons with reduced renal function.

Cephalothin is deacetylated in the liver and other tissues. The resultant deacetylcephalothin accounts for about one third of the antimicrobic activity present in the urine.[49] Since deacetylcephalothin is one half to one sixteenth as potent as cephalothin,[85] considerably more than one third of the injected dose of cephalothin is metabolized. The antibacterial spectrum of deacetylcephalothin is identical with that of cephalothin.[85]

Tubular secretion of cephalothin can be antagonized by probenecid. Renal failure must be extreme before the halflife of cephalothin in the serum is prolonged (Fig. 1). For this reason, only minor modification in dosage is required when renal function is reduced (Table 4).

PREPARATIONS AND DOSAGE. The sodium salt is packaged for injection as a dry, sterile powder in ampoules containing 1 gm. Each gram of sodium cephalothin contains 2.4 mEq. of sodium. For intra-

muscular injection, 1 gm. is dissolved in 4 ml. of water. Dosage is 40 to 80 mg. per kg. body weight per day and is usually given as four to six equal portions injected at 6- to 4-hour intervals. This dose range applies to normal children and adults. In premature and newborn infants, 10 to 15 mg. per body weight per day is sufficient.

For continuous intravenous infusion, sodium cephalothin is dissolved in either 5 per cent glucose or 0.9 per cent sodium chloride solution in a final concentration not exceeding 250 mg. per 100 ml.

ADVERSE REACTIONS. Pain on intramuscular injection is invariable but generally tolerable with 500 mg. or less per injection. Procaine for injection can be used to dissolve cephalothin and does diminish pain. However, with large doses that must be given for a long period of time, intravenous injection is the best resort.

Hypersensitivity to cephalothin is usually manifested by rash—maculopapular or urticarial—although eosinophilia, neutropenia and "serum sickness" have been observed; the incidence is 3 to 5 per cent.[21] Anaphylactic reaction has been reported.[39] Cephalothin is different chemically from the penicillins, and it was hoped that it would not be provocative of hypersensitivity reactions in persons known to be allergic to penicillins. There have been many instances in which this hope appears to have been realized. However, hypersensitivity reactions have occurred on first exposure to cephalothin in persons known to be allergic to penicillin. The evidence regarding cross-allergy, penicillins-cephalosporins, is not yet conclusive, in denial or affirmation.

No reactions of direct toxicity are known. Indeed, toxicologic studies

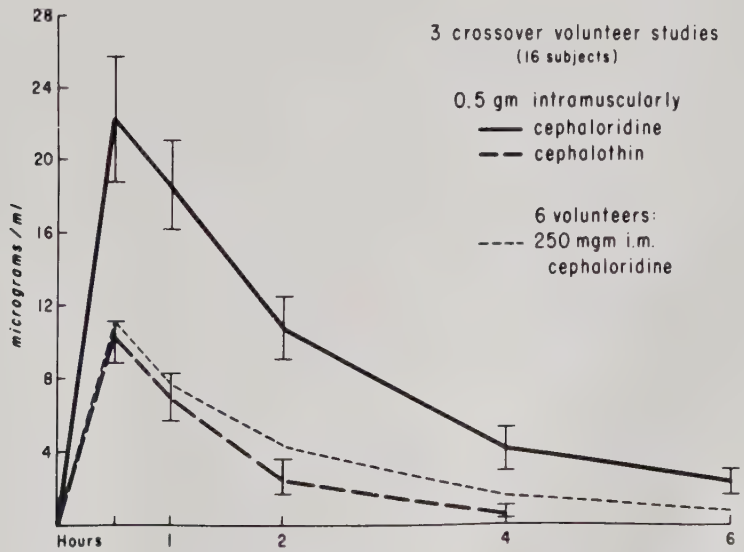

Figure 3. Single intramuscular injections of 0.5 gm. cephalothin and 0.25 gm. cephaloridine yielded virtually identical concentrations in the serum in male volunteers. For equal masses of these two agents, the concentration of cephaloridine in the serum was about twice that of cephalothin. (Reproduced from Figure 1 of Benner et al.[8] by permission of the American Society for Microbiology.)

in animals indicate less toxicity from cephalothin than from benzylpenicillin.

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. While infections caused by gram-positive bacteria are primary indications for use of cephalothin in therapy, there are gram-negative bacilli that are usefully, even uniquely, susceptible to cephalothin. Adding virtual lack of toxicity to the equation forces consideration of therapeutic use of cephalothin for treatment of infections caused by gram-negative bacilli.[30]

Klebsiella sp. Among gram-negative bacilli, Klebsiella sp. are singular in susceptibility to cephalothin.[33, 34] Inability to elaborate a β-lactamase, cephalosporinase, capable of acting on the cephalosporanic acid nucleus, is said to be so regular among Klebsiella sp. as to be an identifying property, setting this genus apart from the other genera composing the tribe Klebsielleae.[25, 26] Whether such a differentiating function is realized or not, there is agreement among most investigators that the majority of clinical isolates of Klebsiella sp. are inhibited by 25 μg. or less of cephalothin per ml. Clinical experience with cephalothin in the treatment of infections caused by Klebsiella sp. has not been extensive. However, results have not been as satisfactory as anticipated from the in vitro studies. Inadequate dosage may be part of the problem; it is likely that 100 to 200 mg. per kg. body weight per day is necessary when there is renal nonurinary tract involvement.

Escherichia coli. Clinical isolates, of intra- and extrahospital origin, are often susceptible to cephalothin. While the frequency of susceptibility appears to vary from one area of isolation and study to another, in the author's experience cephalothin is more likely to be effective than are any of the penicillins, including ampicillin.[34] Large doses must be used in treatment—100 to 200 mg. per kg. body weight—and are best given by continuous intravenous injection.

Proteus mirabilis. As is the case with penicillins, cephalothin has significant antibacterial potency against the indole-negative P. mirabilis.[5] It is so much less active against the other species of Proteus and the Providencia sp. as to be of no value to treatment of infection caused by them. Infrarenal urinary tract infections caused by P. mirabilis, because of concentration of cephalothin in the urine, may respond to doses of 50 to 100 mg. of cephalothin per kg. body weight per day. Renal or extrarenal organ involvement or bacteremia necessitate more vigorous treatment: doses of 100 to 200 mg. per kg. body weight per day.

In the absence of hypersensitivity to penicillins, cephalothin offers no real advantage over the penicillins in the treatment of infections caused by P. mirabilis, except in the occasional instance of a penicillinase-producing isolate.[5] Overall, differences in potency between benzylpenicillin, ampicillin and cephalothin are not so great as to preclude consideration of other factors. With infrarenal urinary tract infection, the convenience of oral therapy recommends ampicillin. When intensive parenteral treatment is required (for renal or extraurinary tract infections), penicillin G is preferable.

Salmonella sp., Shigella sp., Bordetella pertussis and Hemophilus influenzae[74] are susceptible to cephalothin by in vitro testing. There is inadequate clinical experience to permit judgment of effectiveness.

Enterobacter sp., Serratia sp., Pseudomonas sp. and Herrellea sp. are generally resistant to cephalothin, as are enterococcal group bacteria.

NALIDIXIC ACID

Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) is the most active of a series of 1-alkyl-1,8-naphthyridine compounds that have antibacterial biologic activity.[50] Although nalidixic acid has been available since 1962, no other antimicrobics of this chemical variety have appeared.

CLINICAL PHARMACOLOGY. Ordinary doses, e.g., 1.0 gm. in an adult, yield undetectable or very low antibacterial activity in the blood.[12] Note that assay by determination of antibacterial activity uniformly gives much lower values than are obtained by spectrofluorometry, a method of analysis which does not distinguish unchanged, active nalidixic acid from antimicrobially inert metabolites. A preparation for intravenous injection, as yet available only for investigation, yielded concentrations of 10 to 15 μg. per ml. serum (bioassay) 15 minutes after injection of 1.0 gm. of nalidixic acid given as the methylglucamine salt in 500 ml. of 0.9 per cent sodium chloride solution. There was no antibacterial activity in serum obtained 4 hours after injection, by which time virtually all of the drug was in the urine.[87]

The fact of rapid clearance from the blood leads to the expectation that there is no organ localization, save the organs of egress. Small amounts are found in the feces; this may represent biliary excretion. Most of the dose of nalidixic acid is excreted as metabolites, principally glucuronides, that have no antimicrobic activity.[17]

Of the nalidixic acid that is passed in the urine, about 85 per cent is devoid of antimicrobial activity—4 per cent to 5 per cent as a dicarboxylic end-oxidation product and the remainder as glucuronide conjugates of nalidixic acid and hydroxy-nalidixic acid. Unchanged nalidixic acid amounts to about 3 per cent, while unconjugated hydroxy-nalidixic acid accounts for about 13 per cent of the drug that is in the urine.[17] Hydroxy-nalidixic acid is virtually identical in antibacterial spectrum and potency with the parent nalidixic acid. It is probable that oxidation and conjugation are accomplished in the liver, but there is no proof of such hepatic localization of metabolism. Methods of testing urine for glucosuria that depend on reduction, e.g., Benedict's reagent, will yield false positive reactions when patients take nalidixic acid.

PREPARATIONS AND DOSAGE. Presently, nalidixic acid is marketed only as tablets of 250 and 500 mg. The usual oral dose in children and adults ranges from 25 to 50 mg. per kg. body weight per day, given in four equal portions.

A solution for intravenous injection (10 per cent of the methylglucamine salt) may become available in 5 and 10 ml. ampoules. For

intravenous injection, the 10 per cent solution must be diluted in sufficient 0.9 per cent sodium chloride solution or 5 per cent glucose solution to yield 1 to 2 mg. of drug per ml. The total daily dose of 50 mg. per kg. body weight is given in three equal portions at 8-hour intervals, each portion of the dose delivered during a 1 hour period.

When there is impairment of hepatic or renal function, dosage should be reduced or stopped (see Table 4). Onset of neurologic symptoms requires reduction in dosage in such patients.

ADVERSE REACTIONS. Nausea, vomiting and diarrhea have been associated with oral administration of nalidixic acid.

Hypersensitivity is manifested by pruritus, rash and urticaria. In addition, eosinophilia, with and without fever, has been reported.

Drowsiness, weakness, visual disturbances, confusion, hallucinations and seizures form a progression in severity of neurotoxicity. All are completely reversible on reduction or cessation of dosage.

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. Because of very rapid metabolism and urinary excretion, whether given by mouth or by vein, nalidixic acid is useful only in urinary tract infections. The one report of actual concentration of nalidixic acid in the kidneys is specious, for all assays were done by spectrofluorometry.[37] Moreover, there is no support from clinical experience, in that relapse is frequent when pyelonephritis caused by bacteria apparently susceptible to nalidixic acid has been treated with this agent.[12, 69] The area of possible use of nalidixic acid is thus reduced to infranephric urinary tract infections.

Pseudomonas sp. and enterococcal group bacteria are notable among microbial causes for lower urinary tract infections in that they are quite solidly resistant to nalidixic acid.

Almost all of the gram-negative bacilli of the family Enterobacteriaceae are susceptible to nalidixic acid in concentrations well below those achieved in active form in the urine with usual doses. With E. coli the commonest cause of lower urinary tract infections, clinical experience is fully in accord with susceptibility studies—nalidixic acid is effective therapy.[66, 69] However, of itself, good clinical effect does not endorse nalidixic acid as the agent of choice for treatment of such lower urinary tract infections. Among the synthetic antimicrobics, a sulfonamide or nitrofurantoin would serve—at less cost, as conveniently, and with about the same probability of success. Penicillin V or ampicillin have similar advocacy, and may be safer.

A better case may be made for the use of nalidixic acid in the treatment of lower urinary tract infections caused by the indole-positive Proteus sp., Providencia sp., and Enterobacter sp., for these Enterobacteriaceae are usually resistant to most other antimicrobics.

There is yet a significant demurrer: development of resistance in the course of therapy with nalidixic acid. For example, in one study, in 13 of 50 patients (26 per cent), initially susceptible bacilli were replaced with markedly resistant bacilli, of identical species and susceptibility to other agents, within 18 hours of the start of treatment with nalidixic acid.[69]

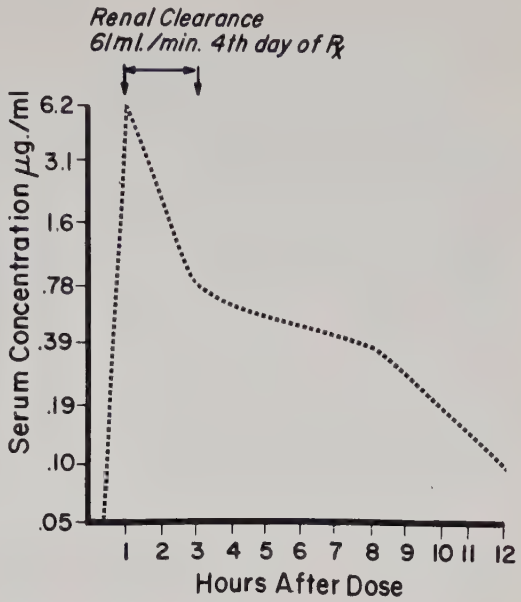

Figure 4. Variation in serum concentration of gentamicin with time after intramuscular injection of 0.8 mg. per kg. body weight. (From Figure 1 of Jao and Jackson[38] by permission of the Journal of the American Medical Association.)

GENTAMICIN

Gentamicin is the newest of the aminosugar antibiotics to succeed to therapeutic use.[84] The entire structure of gentamicin is not yet known, but it is certain that deoxystreptamine is a part of the molecule, as it is with neomycin, kanamycin and paromomycin.

CLINICAL PHARMACOLOGY. Blood concentration is maximal approximately 1 hour after an intramuscular injection,[38] attaining a serum concentration of around 6 μg. per ml. following intramuscular injection of 0.8 mg. per kg. body weight as a single dose (Fig. 4). There is no appreciable degradation or metabolism of gentamicin in the body. The drug is excreted in antimicrobially active form, primarily by glomerular filtration. There is concentration in the urine, so that there are 40 to 50 μg. per ml. when the total daily dose is 2.4 mg. per kg. body weight.[13]

PREPARATIONS AND DOSAGE. For oral administration, capsules containing 25 mg. each have been used. In oral therapy, from 100 to 800 mg. per day is given in divided doses, with the higher dosage reserved for preoperative bowel preparation. An ophthalmic solution, with 0.3 per cent gentamicin sulfate, can be used three to four times per day in one- to two-drop quantities. Topical application, two or three times per day, is possible with two preparations, each containing 0.1 per cent gentamicin: a cream that is water soluble and an ointment that is not miscible with water.

For parenteral injection, gentamicin sulfate is packaged 2.0 ml. per ampoule, with 40 mg. gentamicin base equivalent per ml. The usual dose is 1.5 to 2.0 mg. per kg. body weight per day given in three equal portions at 8-hour intervals by intramuscular injections. This preparation can be injected intravenously if diluted, e.g., 10 mg. per 100 ml. of

5 per cent glucose or 0.9 per cent sodium chloride solution. The parenteral dose must be reduced to compensate for diminished excretion when there is renal insufficiency (see Table 4).

ADVERSE REACTIONS. There are no significant adverse reactions to orally or topically applied gentamicin.

Parenterally administered gentamicin has potential for nephrotoxicity and neurotoxicity. The former is usually mild and is manifested by proteinuria, sometimes with an increase in the blood urea nitrogen. Neurotoxicity takes the form of vestibular damage that may become clinically apparent 1 day to 2 weeks after cessation of treatment—that is, 2 weeks to 5 weeks after initiation of therapy.[38] The anatomical site of injury is not known. While loss in acuity for perception of high tones has been observed after therapy with gentamicin, deafness has not been reported. From past clinical experience with other aminoglycosyl-antimicrobics it is safe to predict that the vestibulotoxic potential of gentamicin is additive to that of streptomycin-dihydrostreptomycin, neomycin, kanamycin and viomycin.

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. Although acid-fast bacilli and gram-positive bacteria are susceptible to gentamicin, safer and equally (or more) effective antimicrobics are available for the treatment of infections caused by these kinds of bacteria.

By in vitro testing, among the aminosugar antimicrobics, only neomycin is more potent against many gram-negative bacilli than gentamicin.[59] The singular aspect of gentamicin which emerges from the many studies of susceptibility that have been carried out is that it is the only single antimicrobic which offers high probability of effectiveness against E. coli, Klebsiella sp., Enterobacter sp. and Pseudomonas sp., as well as all of the Proteus sp. Minimal absorption from the gastrointestinal tract, coupled with broad ranging antibacterial effectiveness, makes gentamicin suitable for suppression of enteric bacteria in preparation for bowel surgery. Gentamicin appears to be adequate for this purpose;[65] it is, however, no better than older, established agents, such as neomycin, and preoperative bowel preparation is not really an indication for use of gentamicin.

Poor absorption and wide antibacterial effectiveness also recommend gentamicin for topical therapy. It has been used in ointment and cream forms in treatment of decubitus ulcers[7] and infected skin wounds[77] with apparent good effect. There is virtually no reported experience with the ophthalmic preparation.

Injected gentamicin has been used most extensively in treatment of urinary tract infections. The correlation of good clinical effect with susceptibility by in vitro testing has been excellent. Thus, nonobstructive urinary tract infections, with or without renal involvement, that are caused by gram-negative bacilli of the family Enterobacteriaceae will usually respond to therapy with gentamicin.[13, 38] Similarly, infections caused by Pseudomonas sp. can be treated successfully with gentamicin. This is not to say that gentamicin is the agent of first choice for therapy. The drug must be injected and it does bear significant toxic hazard. With E. coli there are usually safer, more conveniently used alternatives,

particularly for infranephric urinary tract infections—sulfonamides, nitrofurantoin, nalidixic acid, penicillin V, ampicillin. With Klebsiella sp., nitrofurantoin, nalidixic acid, polymyxin B, and cephalothin are preferable. Penicillin G, ampicillin, and cephalothin are the agents of choice for treating infections caused by Proteus mirabilis. With indole-positive Proteus sp. kanamycin is frequently effective and is probably no more toxic than gentamicin, although gentamicin may prove to be the preferable agent. Providencia sp. appear to be best treated with cycloserine or kanamycin. Often effective against Pseudomonas sp., gentamicin has not been shown to be superior to polymyxin B in potency; moreover the hazard of irreversible toxic effect is greater with gentamicin than with polymyxin B.

Gentamicin given by parenteral injection may have primary indication in sepsis of unknown specific cause. The spectrum of antimicrobial activity of gentamicin alone rivals that of the combination of kanamycin plus polymyxin B, with the advantage of lesser probability of toxic injury. That is, gentamicin by itself is less likely to cause renal tubular injury than is the combination of kanamycin plus polymyxin B; while perhaps no less likely to cause permanent vestibular damage than kanamycin, gentamicin has yet to be associated with incapacitating auditory injury.

CEPHALORIDINE

The second semisynthetic derivative of 7-aminocephalosporanic acid to attain therapeutic use, cephaloridine (7-[2-(2-thienyl)acetamido]-3-(1-pyridy-methyl)-3-cephem-4-carboxylic acid betaine) differs from its predecessor, cephalothin, primarily in pharmacologic properties.[1] Since it is a betaine, in aqueous solutions the cephaloridine molecule supplies its own cation—there is no need for sodium or potassium. Possibly the lessened pain on intramuscular injection, decreased binding to serum proteins, and the slowed excretion, as compared with cephalothin, are also consequences of inner salt formation.

CLINICAL PHARMACOLOGY. Maximal concentration is reached in the blood 15 to 30 minutes after injection; following injection of a single dose of 500 mg. there will be about 20 μg. per ml. serum, with more than 2 μg. per ml. still present 6 hours after injection[8] (see Fig. 3). There appears to be little metabolism of cephaloridine and the unchanged drug is excreted in the urine by glomerular filtration and tubular secretion. Tubular secretion is less active with cephaloridine than it is with cephalothin, apparently accounting for the prolonged high concentrations observed in blood and extracellular fluids. Probenecid will antagonize tubular secretion.[81] There is concentration as urine is formed so that levels of 50 to 1000 μg. per ml. of urine result, varying with dose and with quantity of urine excreted.

PREPARATIONS AND DOSAGE. Cephaloridine is available in ampoules containing 1 gm. of dry powder. For intramuscular injection, the drug is dissolved in 2 ml. of water for injection—addition of a local anesthetic is feasible but is rarely necessary. The total daily dose is 20 to 80 mg. per

kg. body weight in both children and adults. The intramuscular route can be used by giving three equal portions at 8-hour intervals when no more than 1.0 gm. is delivered per injection. With larger total doses, or when intramuscular injection is not feasible, constant intravenous infusion of cephaloridine in either 0.9 per cent sodium chloride or 5 per cent glucose solutions (100 to 250 mg. cephaloridine per 100 ml.) is effective and well tolerated.

ADVERSE REACTIONS. Pain after intramuscular injection of cephaloridine is generally not a major complaint.

Hypersensitivity reactions, consisting of skin rashes, fever and granulocytopenia, have been reported. Use in patients with histories of allergic reactions to penicillins has not been extensive; as in the early experience with cephalothin, there does not appear to be cross-hypersensitivity.[48] Caution on this point must be observed; not only are observations limited, but also persons who have once manifested a drug allergy are likely to do so again.

Renal tubular necrosis resulted in experimental animals given very large doses of cephaloridine.[71] When there is impairment of renal function in humans, it is conceivable that inefficiency in excretion of cephaloridine could lead to nephrotoxicity, although there have not been reports of such toxic effect in humans. For this reason, reduced renal function requires compensatory reduction in dosage when cephaloridine is used[71] (see Table 4).

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY. Cephaloridine appears to be applicable to therapy in the same situations in which cephalothin is useful, i.e., principally infections caused by gram-positive bacteria. Among gram-negative bacilli, most clinical isolates of Escherichia coli are susceptible to cephaloridine; however, when there is infrarenal urinary tract infection, many agents that can be given by mouth are equally effective and are more convenient to use. When E. coli is the cause of renal or extrarenal infections, cephaloridine might be preferable to cephalothin for therapy, since dosage would be (1) smaller—less drug per injection and fewer injections; (2) free of unwanted cation; and (3) less painful.

Although clinical isolates of Proteus mirabilis are usually susceptible to cephaloridine, infections caused by these gram-negative bacilli are generally treated with penicillin G. However, when hypersensitivity precludes use of penicillins, cephaloridine is likely to be a suitable alternative.

Klebsiella sp. and Hemophilus influenzae are susceptible to cephaloridine by in vitro testing. There is insufficient clinical experience to know what the place of cephaloridine will be with infections caused by these kinds of bacilli.

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Newer and Second-Line Drugs in the Treatment of Drug-Resistant Tuberculosis in Children

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Great success has been achieved in the treatment of previously lethal forms of tuberculosis in children with the three major antituberculous drugs, streptomycin, isoniazid and para-aminosalicylic acid (PAS). However, the emergence of drug resistant strains of Mycobacterium tuberculosis in the adult has caused concern about the transmission of such strains to children.

While it has been demonstrated that isoniazid-resistant strains of M. tuberculosis may have attenuated virulence for guinea pigs and mice, it has been definitely established that they can cause active disease in children[16, 87, 102] and at times fatalities,[16, 25, 50, 102] thus indicating the necessity for the employment of other effective antituberculous drugs. Fortunately, such drugs are available and are commonly referred to as the newer or second-line drugs.

Extensive studies have been made in adults of the therapeutic effectiveness, dosage schedules and toxicity of various combinations of these drugs in the treatment of chronic pulmonary tuberculosis. As a result of these studies, the Committee on Therapy of the Medical Section of the National Tuberculosis Association has recommended criteria for their use in adults,[60] which may be applied to children with infection due to drug-resistant organisms. These are:

1. Therapy must be based on current drug susceptibility tests.
2. At least two drugs to which the infecting strain of tubercle bacilli is susceptible should be added to any regimen. The addition of a single new drug at any time is strongly condemned. If partial susceptibility to isoniazid is present, then this drug may be continued in the regimen.
3. The physician must be familiar with untoward reactions and potential toxic effects of all the drugs used. Daily observations must be made for signs of clinical toxicity and laboratory tests for untoward effects of specific drugs.

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4. Combinations of drugs which produce similar toxic effects, such as deafness or liver or renal damage, should be avoided unless no other combination is possible.

5. For adults with chronic pulmonary disease, a minimal period of 6 months of hospitalization is recommended until clinical stability is solidly established, and a period of one year of treatment after reversal of infectiousness is obtained. The patient must be observed closely with continuing laboratory studies.

Two main difficulties present themselves with the use of these drugs in children. The first is related to the isolation and susceptibility testing of the infecting strain of organism in the child. In the adult, where organisms can be readily isolated and susceptibility tests made by the direct method, results can be obtained within three weeks. In the child with such rapidly lethal forms of disease as acute miliary tuberculosis or meningitis, few colonies are obtained on primary culture from gastric washings or spinal fluid, and susceptibility tests must be done by the indirect method, requiring about eight weeks. In our clinic, we have been able to obviate this difficulty in instances where susceptibility tests on the source case strains were available to us. In matching susceptibility tests on 46 source case strains with those of the infecting strain of M. tuberculosis in children, a high degree of correlation was obtained (unpublished data).

The second difficulty in the use of these drugs in children is related to dosage. While some of these drugs have been used in children, none has received the critical evaluation regarding dosage schedules that are available for adults.[4, 18, 29–31, 34–36, 70, 75] From the meager reports available, it appears that children tolerate these drugs better than adults and have fewer toxic reactions. A method for estimating dosage in children, based on the adult dose, is presented later.

With these difficulties stated, this paper presents a description of the second-line or newer drugs and their use in children where the infecting strain of M. tuberculosis is resistant to the three major drugs.

Prior to 1960, the second-line drugs available for use were viomycin, pyrazinamide, cycloserine and kanamycin. To these have been added ethionamide, capreomycin and ethambutol.

Viomycin

Viomycin is an antibiotic agent introduced in 1950 and produced from an actinomycete named Streptomyces puniceus.[27] It has a low toxicity for mice, rats and dogs[27] and is equally effective in vitro against streptomycin sensitive and resistant strains of M. tuberculosis.[3, 21, 38] It is highly effective in retarding experimental tuberculosis in guinea pigs and mice, and is reported to be comparable in effectiveness to streptomycin.[40, 83, 101]

When used alone, this drug is reported to have an appreciable antituberculous action in man, but it is less effective than either streptomycin or isoniazid.[73, 91] It has its greatest usefulness in combination with other antituberculous drugs when resistance to the three major drugs is present.[1, 65, 73, 79, 91, 97]

Toxic manifestations in man are those of renal irritation (slight elevation of blood urea nitrogen), vestibular damage, deafness, dis-

turbances in electrolyte balance (hypocalcemia, hypokalemia, hypophosphotemia, hypochloremia, increase in carbon dioxide combining power) and minor hypersensitivity reactions. However, these toxic effects are not of sufficiently serious degree or character to prevent the use of this drug.[1, 73, 97] Monthly audiograms and blood urea nitrogen determinations should be done to check for toxic effects.

Viomycin is given by intramuscular injection in adults in doses of 15 to 20 mg./kg. in two divided doses five days a week for four months, depending on the tolerance of the patient.

This drug has been used in children, but no large scale reports are available concerning its effectiveness or toxic reactions. There is a report by Lythcott[51] of a severe anaphylactic reaction occurring in a 12 year old female child who had been treated for chronic pulmonary tuberculosis with daily injections of viomycin (20 mg./kg.) and pyrazinamide (35 mg./kg.) for seven weeks. Skin tests proved the reaction to be due to viomycin. The child recovered after symptomatic treatment for allergic shock.

Viomycin can be used in combination with isoniazid, PAS, ethionamide, pyrazinamide, cycloserine or ethambutol. It is the least effective of the injectable antituberculous drugs and should be given only when adequate susceptibility to it has been demonstrated.

Pyrazinamide

Pyrazinamide is an antituberculous chemotherapeutic agent first synthesized in 1952, chemically related to the thiosemicarbazones and nicotinamide.[46]

In vitro, pyrazinamide inhibits virulent strains of M. tuberculosis in concentrations of 10 μg./ml. at pH 5.2 to 5.3.[85, 95]

In vivo, pyrazinamide has been shown to exert a moderate degree of antituberulcous activity in experimental tuberculosis in mice and guinea pigs.[17, 52] However, combinations of pyrazinamide with isoniazid were demonstrated to be more effective than either drug used alone.[54]

Early clinical trials of pyrazinamide in the adult, as a single drug treatment, showed it to be clinically effective in patients whose tubercle bacilli were either streptomycin resistant or sensitive, but its usefulness was limited by the rapid emergence of strains resistant to the drug.[52] Tried in various combinations with isoniazid, streptomycin or PAS, it was found to be highly effective in the treatment of chronic pulmonary tuberculosis in the adult.[9, 12, 53, 55, 78, 95]

Reports of toxic effects vary from negligible[9, 12, 78, 100] to serious liver damage.[53, 55] In a large scale study by the United States Public Health Service,[93] it was concluded that liver damage was the main manifestation of toxicity and was dose related. Twelve weeks of treatment with either 25 or 40 mg. of pyrazinamide per kg. of body weight produced evidence of liver damage in 2 to 3 per cent of patients, whereas 40 mg./kg. of body weight for 24 weeks increased the incidence to 6 per cent.

Serum uric acid levels were also reported to be high in some cases.[53]

Serum glutamic oxaloacetic transaminase and uric acid levels should be determined every three weeks to monitor toxic effects.

This drug is effective in combination with other antituberculous drugs in the treatment of infection due to organisms resistant to the three major drugs. It should be used in combination with one or two other drugs which are not hepatotoxic, such as kanamycin, cycloserine, viomycin or ethambutol.

Pyrazinamide is given orally, and the usual dose for adults is 3 gm. per day in four divided doses. Suggested dose for children is 20 to 30 mg./kg. per day given in three divided doses.

Cycloserine

Cycloserine is an antibiotic first described in 1955, produced by Streptomyces orchidaceus.[96] It is water soluble and of low molecular weight. In vitro, virulent strains of M. tuberculosis are inhibited by concentrations of 20 μg./ml. of the drug. In vivo tests in experimental tuberculosis showed cycloserine to be ineffective in controlling the disease in guinea pigs when used alone.[62, 63, 84] However, combinations of isoniazid with cycloserine were slightly more effective than isoniazid used alone.[98]

The drug was first tried clinically by Epstein and his co-workers,[22] who reported it to be effective in the treatment of 29 cases of pulmonary tuberculosis in adults whose organisms had become resistant to streptomycin and isoniazid. Subsequent reports have shown that cycloserine has its most effective use in combination with isoniazid,[2, 8, 24, 39, 48, 72] pyrazinamide[32, 68] or viomycin.[79]

Toxic effects of cycloserine are reported to be proportional to the dosage used and presumably to blood concentration.[67] These effects are related mainly to the central nervous system and include muscle weakness, twitchings, tremors, poor coordination, hyperreflexia, ankle clonus, dysarthria, visual disturbances and convulsions.[23, 67] Psychic effects such as nervousness and irritability, psychotic states with suicidal tendencies, and paranoid, catatonic and depressed states are also reported in adults.[67]

This drug is given orally and the suggested dose in adults is 250 mg. four times a day. Adjuvant medications such as pyridoxine, tranquilizers, phenobarbital and diphenylhydantoin are said to control the toxic manifestations, which are reversible on cessation of the drug.[23, 67]

Cycloserine has been used in children in combination with isoniazid in two small series of cases totaling 29 children.[4, 75] The dosage used in one series was 15 mg./kg. body weight, which produces blood serum levels of 3 to 36 μg./ml.[75] In the other series a dosage of 20 mg./kg. of body weight produced blood serum levels of 35 μg./ml. The striking feature of both series of cases was the absence of any toxic effects. No concomitant medications were given in either group.

Kanamycin

Kanamycin is a water soluble basic antibiotic first isolated in 1958 by Umezawa[92] from broth cultures of Streptomyces kanamyceticus. It is

active against mycobacteria as well as gram negative and gram positive organisms. Its action is bactericidal and it is more active against proliferating than against resting cells. It is well absorbed following intramuscular and subcutaneous administration but is poorly absorbed when given orally.

In vitro, kanamycin is effective against streptomycin, isoniazid and PAS sensitive and resistant strains of M. tuberculosis. In experimental infection in guinea pigs, its activity has been reported by some observers to be almost of the same order as that of streptomycin and isoniazid.[99] Other observers have found it to be less active in similarly produced infection than isoniazid and only slightly less so than streptomycin.[86]

In the adult, this drug has been used effectively in combination with other antitiberculous drugs in the retreatment of chronic pulmonary tuberculosis where the infecting strain of M. tuberculosis had become resistant to the three major drugs.[14, 41–44]

Nephrotoxicity (proteinuria, fine granular casts, red blood cells) is a frequent finding but is generally transient and reversible. The major toxic effect is deafness, which is generally irreversible and it is related to the total dose, renal functional impairment, duration of treatment and pre-existing hearing loss.[26]

Minimal inhibiting concentration for M. tuberculosis is 2.0 μg./ml. and desirable six hour serum level 20 μg./ml. This can be achieved in the adult by a dosage of 20 mg./kg. given in two doses intramuscularly three hours apart. Suggestive duration of treatment in the adult is four months with the drug administered five days a week.[42]

Kanamycin has been used by High[34, 35] in the treatment of 22 children with various forms of tuberculosis. All children recovered, but it is difficult to assess the clinical effectiveness of kanamycin, because it was used in combination with isoniazid and no mention was made of the susceptibility of the infecting organisms. Dosage of kanamycin varied from 8 to 90 mg./kg. per day; most children received 10 to 25 mg./kg. per day. Twenty-one patients were treated for two to eight months, and 14 of these subsequently received kanamycin weekly for four weeks to six months. Serum levels after 15 mg./kg. intramuscularly reached peak levels of 32 μg./ml. at one hour and then dropped to 4 μg./ml. at six hours.

All but three patients had small numbers of casts, red blood cells and white blood cells in the urine and in a few instances traces of protein, but the drug was not discontinued because of these findings. There were no elevations of blood urea nitrogen.

Gross hearing abnormalities were noted in only two patients, one with pre-existing purulent otitis media and the other with tuberculous meningitis. In two patients who received 25 to 90 mg./kg. per day there was definite loss of high tone when first tested, one after 62 days of treatment with 90 mg./kg. and the other with 25 mg./kg. after 148 days of treatment. These did not get worse, nor did they improve subsequently.

In younger infants, who were difficult to test audiometrically, it was observed that they continued to respond appropriately to conversational

tones and that they acquired new language functions during long term administration of the drug. It was suggested from these observations that they had not suffered any significant hearing loss, at least at 4000 cycles a second, and that infants and children have less risk of hearing loss following the use of kanamycin than adults.[36]

This drug should be used in combination with two other drugs to which the infecting strain of M. tuberculosis is susceptible, the preferred drugs being either ethionamide and cycloserine, since these can be given orally and are neither nephrotoxic nor ototoxic, or pyrazinamide and ethambutol, for the same reasons.[26]

Monthly determinations of blood urea nitrogen and audiograms should be obtained to check for renal and ototoxic effects.

The suggested dose for children is 15 mg./kg. given intramuscularly in two divided doses, five days a week for four months.

Ethionamide

Ethionamide is an antituberculous chemotherapeutic agent first synthesized in 1962, as a derivative of isonicotinic acid. It differs from isoniazid in that it does not contain the hydrazide chain. It is active in vitro as well as in vivo against isoniazid sensitive or resistant strains of M. tuberculosis and is said to exert a bactericidal effect only on actively growing cells.[71] Its suggested mode of action is the inhibition of protein synthesis in the cell.[90]

In experimentally induced tuberculosis in guinea pigs, ethionamide was reported to be twice as effective as streptomycin and one tenth as effective as isoniazid.[71]

In vitro, the minimum inhibitory level of ethionamide ranges from 0.6 to 1.2 μg./ml.[71] After ingestion in man the drug is readily absorbed. Active serum concentrations of 12, 6 and 3 μg./ml. are obtained at three, six and nine hours, respectively, after oral administration of 0.5 gm. of the drug.

In vitro, cross resistance to ethionamide with isoniazid, PAS, streptomycin, viomycin or cycloserine does not occur.[71]

Clinical trials in adults indicate that ethionamide should not be used alone, either as initial therapy or in retreatment therapy. It appears most effective when used in combination with other antituberculous drugs.[6, 13, 56, 64, 81]

Toxic effects of this drug are mainly due to gastric intolerance (nausea, vomiting and anorexia) and liver damage. The latter has been described as ethionamide-induced hepatitis and is estimated to occur in about 5 per cent of the cases treated.[11] Signs of liver toxicity subside promptly with cessation of the drug and may recur with its readministration.

The adult dose is 1 gm. daily, given orally in four divided doses. Serum glutamic oxaloacetic transaminase determinations should be made every two to three weeks to test for liver toxicity.

Ethionamide has been used in the treatment of various types of tuberculosis in children in combination with isoniazid or PAS. It ap-

pears to be clinically effective when used in combination with other antituberculous drugs, but no randomized studies are available in children for comparison. Children tolerate ethionamide better than adults and the incidence of toxic effects is much less frequent.[18, 29–31] Its use should be limited to treatment of severe tuberculous infections with drug-resistant strains of M. tuberculosis, and it should be given in combination with other antituberculous drugs that are not hepatotoxic, such as kanamycin, cycloserine, viomycin, capreomycin or ethambutol (when the latter two drugs are available). The suggested dose for children is 10 to 12 mg./kg. given in three divided doses orally.

Ethambutol

Ethambutol is a new synthetic compound chemically unrelated to any other antituberculous drug. It was first described in 1961 as the dextroisomer of 2,2[1]-(ethylenediimino)-di-1-butanol dihydrochloride. In vitro strains of M. tuberculosis are inhibited by the drug at concentrations of 1 μg./ml. in standard culture media. It is equally effective against sensitive as well as isoniazid- and streptomycin-resistant strains of M. tuberculosis.[89]

Ethambutol is said to exert its antimicrobial effect by interfering with the synthesis of metabolites required for cell multiplication, since it acts only on actively proliferating cells.[45] It enters the mycobacterial cell by diffusion and is bound to the cell, which becomes deficient in RNA. It is suggested that ethambutol may act by interfering with the role of polyamines and magnesium ions in the cells, leading to disturbances in nucleic acid metabolism.[28]

In vivo, ethambutol is effective against experimental tuberculosis in mice when given either orally or parenterally. On an oral dose basis, the efficacy index (tolerance/potency) of the drug is said to be similar to that of isoniazid, and parenterally it is superior to streptomycin.[89] It is compatible in combinations with isoniazid and streptomycin. In experimental tuberculous infection in the monkey, low doses of ethambutol combined with low doses of isoniazid produce therapeutic results strikingly better than when either compound is given alone.[77]

After oral administration, ethambutol is rapidly absorbed and peak serum concentrations appear most frequently four hours after ingestion. About 10 per cent of the drug is metabolized to an inactive form and 60 to 80 per cent is excreted unaltered in the urine. Therapeutic peak serum levels range from 3 to 5 μg./ml.[66]

Clinically, ethambutol has been used in the retreatment of chronic pulmonary tuberculosis in the adult. When it is used alone, therapeutic activity, as measured by conversion of sputum, occurs within three months in the majority of patients on daily doses of 25 mg./kg. However, bacteriological relapses occur and ethambutol-resistant strains develop in about 35 per cent of the cases.[66] When used in combination with other antituberculous drugs to which the infecting strain of M. tuberculosis is sensitive, excellent clinical responses have been obtained and bacteriological relapses have for the most part been prevented.[5, 15, 19, 49, 66, 69, 70]

Toxic effects of ethambutol have been limited to disturbances in visual acuity, as evidenced by blurred vision and the concurrent loss of ability to see green color.[47] The occurrence of these symptoms is related to total dosage of the drug, and they disappear when the drug is discontinued.[5, 49]

Pyle[70] has reported the use of ethambutol in combination with cycloserine in the treatment of a five year old white male child who had disseminated tuberculosis. The infecting strain of M. tuberculosis was resistant to the three major drugs. The child appeared to be in critical condition until the institution of therapy with ethambutol and cycloserine in dosages of 20 and 30 mg./kg. respectively. The drugs were well tolerated and the patient made a dramatic recovery. In vitro, the patient's strain of tubercle bacilli was highly sensitive to both drugs used. He had been treated in the hospital for nine months and it was planned to continue therapy for at least two more years.

The adult dose of ethambutol is 25 mg./kg. per day given in two divided doses orally for 8 to 12 months. Multivitamins are given concurrently with the drug. Tests for visual acuity and color vision should be done before and during administration of the drug.

Ethambutol has not been approved as yet by the Food and Drug Administration, but all of the clinical reports indicate that it is a good companion drug for isoniazid and perhaps useful as a replacement for PAS or in combination with other antituberculous drugs when the infecting strain of M. tuberculosis is resistant to the three major drugs.

The suggested dose for children is 20 mg./kg. given orally in two divided doses.

Capreomycin

Capreomycin is an antituberculous antibiotic isolated in 1960 from a new species of streptomycete, termed Streptomyces capreolus.[33] It is a water soluble complex of four peptide entities with demonstrated antibiotic activity in vitro and in vivo against test strains of M. tuberculosis.[59, 88]

Minimum inhibitory concentrations of the drug are reported to be 0.485 μg./ml.[59] to 2.0 μg./ml.,[88] depending on the technique used for testing. Morse and his co-workers[59] report that the minimum inhibitory level of capreomycin, microgram for microgram, is approximately one half that of streptomycin, kanamycin, ethambutol and PAS, one tenth that of isoniazid, and one half that of ethionamide. No cross resistance was found between strains of M. tuberculosis either sensitive or resistant to isoniazid, streptomycin, PAS, ethionamide or kanamycin. However, strains of M. tuberculosis resistant to capreomycin were found to be resistant to viomycin, but strains resistant to viomycin were not resistant to capreomycin.

Clinically, capreomycin has been used in the treatment of pulmonary tuberculosis in the adult in combination with other antituberculous drugs and reported as an effective therapeutic agent.[7, 10, 20, 57, 58, 74] Its activity has been comparable in many respects to that of streptomycin.[80]

The toxic effects of capreomycin are similar to those of kanamycin and streptomycin and are related to damage of the auditory branch of the eighth nerve and of the kidney. However, under controlled conditions these changes are not sufficient to proscribe the use of this drug.[7, 10, 20, 57, 58, 74] Monthly determinations of blood urea nitrogen and audiograms should be done to monitor patients receiving the drug.

Capreomycin has only weak activity when given orally, since it is almost completely destroyed in the stomach. Administration of 1 gm. of the drug intramuscularly produces effective serum levels for at least four hours.

The dosage schedule for adults is 15 to 20 mg./kg. per day, given intramuscularly in two divided doses five days a week for four months. It has been suggested as a substitute for streptomycin and should be given in combination with other antituberculous drugs such as ethionamide, pyrazinamide, cycloserine, ethambutol, isoniazid or PAS, which are neither ototoxic nor nephrotoxic.

Suggested dosage for children, based on adult values, would be 15 mg./kg. body weight, given intramuscularly in two divided doses daily for four months.

This drug has not yet been released by the Food and Drug Administration but appears to have favorable endorsement by many investigators in the field of tuberculosis.

Summary and Comment

Isoniazid, streptomycin and PAS remain the drugs of choice in the treatment of all forms of tuberculosis in children. However, when strains of tubercle bacilli resistant to these drugs have been demonstrated as the infecting organism, second-line drugs should be employed and so selected as to avoid the use of combinations of drugs with similar toxic effects. There is experimental evidence to show that isoniazid may be useful in the drug regimen even though the infecting strain of tubercle bacillus is resistant to isoniazid.[61, 76]

In Table 1 are given the usual dosage for adults and suggested dosages for children, with the second-line drugs grouped according to their major toxic effects. In Table 2 are given the hypersensitivity reactions usually associated with these drugs.

The schedules for adults have been derived from extensive clinical trials, whereas the suggested dosages for children are derived from the adult dosages and are based on body weight alone. From the small number of reports in the literature, these dosages appear to be effective and children have fewer toxic reactions than adults. Actually, drug dosages for children derived from adult values based on body weight alone, without correction for body surface area or metabolism, will give smaller values than when these factors are taken into consideration. In critically ill patients in whom it is desirable to give maximum dosages of these drugs, correction for these factors can be made by several methods. The "corrected body weight method" as described by

Table 1. *Second-Line Antituberculous Drugs Grouped According to Major Toxic Effects**

DRUG	USUAL ADULT DOSE AND ROUTE OF ADMINISTRATION		SUGGESTED DOSE FOR CHILDREN†		MAJOR TOXIC EFFECTS
Viomycin	15–20 mg./kg./24 hours (Vial: 2.0 ml. = 1 gm.)	Intramuscularly in 2 divided doses 5 days a week for 4 months	15 mg./kg./24 hours	Intramuscularly in 2 divided doses 5 days a week	Ototoxic, nephrotoxic
Kanamycin	15–20 mg./kg./24 hours (Vial: 3.0 ml. = 1 gm.)		15 mg./kg./24 hours		Ototoxic, nephrotoxic
Capreomycin‡	15–20 mg./kg./24 hours (Vial: 3.0 ml. = 1 gm.)		15 mg./kg./24 hours		Ototoxic, nephrotoxic
Pyrazinamide	3.0 gm./24 hours (Tablet = 0.5 gm.)	Orally in 4 divided doses	20–30 mg./kg./24 hours	Orally in 3 divided doses	Hepatotoxic; uric acid elevations
Ethionamide	1.0 gm./24 hours (Tablet = 0.25 gm.)		10–12 mg./kg./24 hours		Hepatotoxic; gastrointestinal disturbances
Cycloserine	1.0 gm./24 hours (Capsule = 0.25 gm.)	Orally in 4 divided doses	15 mg./kg./24 hours	Orally in 2 divided doses	C.N.S. toxicity: convulsions, psychotic reactions
Ethambutol‡	25 mg./kg./24 hours (Tablet = 0.4 gm.)	Orally in 2 divided doses	20 mg./kg./24 hours		Neurotoxic: optic nerve (blindness)

*Avoid combinations of drugs with similar toxic effects.

†Dosage for children based on adult dosage uncorrected for surface area and metabolism.

‡Not released as yet by Food and Drug Administration.

Table 2. *Hypersensitivity Reactions to Second-Line Antituberculous Drugs**

DRUG	REACTIONS
Viomycin	Fever, rashes, enlarged lymph nodes, leukopenia, anaphylactic shock†
Kanamycin	Fever, skin rashes, eosinophilia, sterile abscess at site of injection
Capreomycin	Fever, eosinophilia (rare)
Pyrazinamide	Slight febrile reactions, skin rashes (bullous eruptions), photosensitivity reactions, minor joint pains
Ethionamide	Skin rashes, serum sickness-like reactions (fever, joint pains), photosensitivity reactions
Cycloserine	None reported
Ethambutol	Fever, rash, pruritus (rare)

*Reported mostly in adults.

†One case reported in a child.

Hildick-Smith[37] has the advantage of simplicity. The calculation is made as follows.

$$\text{Adult dose} \times \frac{\text{weight of child in kg.}}{70} \times \text{correction factor}$$

Correction Factor for "Metabolism"

WEIGHT GROUP	QUALITATIVE CORRECTION FACTOR FOR METABOLISM
Under 6 kg.	2.5
Under 16 kg.	2.0
Under 36 kg.	1.5
Under 56 kg.	1.25
Under 106 kg.	0.75

It must be kept in mind that there are no rules or methods of calculation of drug dosage that can anticipate all variables and "the correct dose for all ages of man, which is enough but not too much, must be determined and adjusted for each particular patient by the physician."[82]

It must be emphasized again that constant vigilance must be maintained for the development of toxic and hypersensitivity reactions to all drug therapy continued for prolonged periods.

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Newer Drugs in the Treatment of Chronic Bronchitis

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The recent resurgence of interest in chronic bronchitis as an important disease entity has stimulated interest in the development of new therapeutic agents and in a better understanding of older agents. Despite the interest, the development of decisively important drugs for chronic bronchitis has not been forthcoming. The lag between interest and results is undoubtedly due to the lack of definitive information as to etiology, pathophysiology, and perpetuating factors of the disease. Nevertheless, some advances in the treatment of chronic bronchitis have been made. Newer agents have offered a few distinct advantages either because of greater efficacy or by offering a greater choice of agents available to perform a given function. Most therapy in chronic bronchitis remains symptomatic.

As a rule, the majority of the investigations carried out on the newer agents have not been significantly improved over the studies of five or ten years ago because of their dependence on subjective evaluations. When objective data are recorded, they often do not relate directly to the claimed action of the agent. Sometimes a restricted point of view as to expected mechanism of action of a new agent hinders thorough pharmacologic studies. For many of the clinical and pathophysiologic characteristics of chronic bronchitis, adequate objective tests have not been developed with which to record the pertinent changes that are expected with the action of the agent. It is important to keep in mind the state of the art of clinical pharmacology in chronic bronchitis in the subsequent discussions of the usefulness of the new therapeutic agents. The lack of standardized and validated means for objectively measuring changes of sputum thickness or stickiness restricts many investi-

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gators from properly evaluating the action of mucolytic or expectorant agents. The lack of means to record objectively frequency and intensity of chronic cough under actual living conditions in patients with pathologically related cough has impeded the proper clinical evaluation of antitussive agents. The means of assessing levels of infection or inflammation in patients with chronic bronchitis are not readily available, so that too many of the evaluations of antibiotics have depended on subjective symptoms, sputum cultures, sputum volumes, and changes in gross appearance of the sputum. The results of such studies are not always easy to evaluate.

Before discussing specific new agents, it is pertinent to remind the reader of an important, nondrug therapeutic measure of importance in chronic bronchitis. Probably the most significant treatment in chronic bronchitis is the avoidance of inhaling irritating and toxic pollutants into the lungs. In many cases of early or simple bronchitis, elimination of such stimuli can result in complete or partial reversibility of the disease process. Consequently, the avoidance of inhaling tobacco smoke is still the single most important therapy that one can institute in chronic bronchitis. The avoidance of air pollution may be more difficult for the individual patient since this often depends on the efforts of the society in which he happens to reside.

The general approach to the diagnosis and treatment of chronic bronchitis has been discussed previously.[1] Some of the newer agents that have been introduced more recently for therapy in chronic bronchitis will be evaluated individually in this report.

AMPICILLIN

Ampicillin, D-alpha-aminobenzyl penicillin, is a unique new synthetic penicillin. It is water soluble and acid stable and has low toxicity. It is readily absorbed after oral administration (average serum levels of over 6 μg./cc. within two hours of 1 gm. oral dose) and can also be given by the intramuscular route. The principal rationale for its use in chronic bronchitis is its antibacterial activity against many gram negative organisms, including Haemophilus influenzae, as well as good activity against the gram positive group of bacteria. It is bactericidal against H. influenzae at reasonable concentrations, which can often be attained by acceptable dosage schedules. Since H. influenzae and Diplococcus pneumoniae are the principal pathogens in chronic bronchitis, the use of ampicillin would appear to be logical and indicated. Ampicillin is rapidly excreted in the urine and concentrated in the bile. More important, it is excreted in the sputum, but in variable concentrations. Studies by May[2] on levels of ampicillin in sputum on a dosage schedule of 1 gm. every six hours in patients with chronic bronchitis have suggested that there is a limitation of usefulness; good levels attained in purulent sputa (0.39 μg./ml.) fell off to probably inadequate levels in mucoid specimens (0.14 μg./ml.). This variation in excretions of the agent in the sputum must be considered in utilizing ampicillin in patients with chronic bronchitis. Other than its anti-

bacterial action against Haemophilus influenzae, ampicillin has clinically significant activity against the majority of the other bacteria considered to be important in chronic bronchitis. The notable exceptions are the Klebsiella-Aerobacter group and Bacillus pyocyaneus, which are virtually unaffected by ampicillin.

Since ampicillin has been introduced it has been found useful in a wide variety of infectious diseases. It has received particular attention because of its potential action in chronic bronchitis. Trafford et al.[3] report the uniformly good response of five cases of Haemophilus influenzae pneumonia. These patients received doses of 0.5 to 1.0 gm. four times daily for five to seven days. Grant et al.[4] compared the use of ampicillin and tetracycline in acute exacerbations of chronic bronchitis using doses of 250 mg. four times a day and noted equally good results with both antibiotics, but no distinct advantage to either. In a study of the treatment of acute exacerbations of chronic bronchitis with ampicillin as compared to demethylchlortetracycline or phenoxymethylpenicillin with streptomycin by Ayliffe and Pride,[5] the authors could detect no advantage of ampicillin when given 500 mg. every six hours for five or more days. They found it to be as effective as the other agents. Millard and Batten[6] compared ampicillin and tetracycline in long-term antibiotic therapy in chronic bronchitis using doses of 500 mg. twice a day. Both regimens produced similar results except that ampicillin treatment was associated with a greater reduction of sputum volume. Both decreased the incidence of H. influenzae in the sputum without significant occurrence of resistant organisms. Most of these results[4–6] are somewhat disappointing because ampicillin can be bactericidal in adequate concentrations, and development of resistance to ampicillin by streptococci, pneumococci, and H. influenzae has not been noted. It would appear from May's studies[2] that the dosage schedules used were generally too low. Also, the most effective period of therapy appears to be while the sputum is still purulent, since as soon as the sputum becomes mucoid the concentration of ampicillin in it decreases. The recommended dose for an acute exacerbation of chronic bronchitis appears to be 1.0 gm. every six hours for about seven days. The indications for choosing ampicillin over tetracycline would be an exacerbation in which H. influenzae is the predominant organism, or a mixed infection with Diplococcus pneumoniae, and when oral therapy is particularly desired. Ampicillin is also indicated in patients with chronic bronchitis with purulent sputum without an acute exacerbation when these two organisms are present in significant numbers. Ampicillin given in this high dosage schedule may be the treatment of choice in these two situations. However, further studies will be required to clarify this point. It certainly should be given when adequate tetracycline therapy has failed to control the H. influenzae, whereas previously chloramphenicol may have been resorted to. Whether ampicillin has a routine place in long-term antibiotic therapy of chronic bronchitis is not clear. If further evaluation supports the results of Millard and Batten, then the less expensive drug of choice would continue to be tetracycline.

Ampicillin is contraindicated in patients with hypersensitivity to

penicillin and in infections wih penicillinase-producing organisms. Allergic reactions, such as seen with other penicillins, have been reported and should be treated in the usual manner. Gastrointestinal disturbances including flatulence, cramping, diarrhea, nausea, and vomiting occur, but may be less frequent than with tetracycline. Since some transient elevations of serum glutamic oxaloacetic transaminase have been noted in infants, the possibility of hepatotoxicity should be kept in mind.

In summary, although further evaluation of efficacy and safety in chronic bronchitis is needed, it appears that ampicillin is a useful addition to the antibacterial therapy in this disease. At the present time tetracyclines remain the first drug of choice for long-term therapy and probably also for acute exacerbations of bronchitis due to H. influenzae. However, ampicillin may assume this position and this antibiotic is certainly the second drug of choice.

METHACYCLINE

Methacycline, a new member of the tetracycline family, has recently been introduced and is said to be more potent than demethylchlortetracycline or tetracycline. Chemically, it is 6-methylene-5-oxytetracycline. Although there are no reports of its specific usefulness in chronic bronchitis, some of the reported pharmacologic and clinical characteristics indicate potential advantages in this disease.[7] Methacycline demonstrates the usual tetracycline spectrum of activity in vitro and in vivo, but the level of activity appears to be greater than that of other tetracyclines. Oral therapy with this agent produces comparable or even higher serum levels than with other tetracyclines and it has a prolonged serum half-life. These two features may permit therapy to be given on a 12 hour schedule and therapeutic levels may persist for 24 to 36 hours after discontinuation of therapy. The rationale for its use in chronic bronchitis is the same as for other tetracyclines, i.e., its relative safety and its efficacy against most of the organisms of consequence in this disease. The clinical indications are similar to those described for ampicillin. Adequate dosage schedules have not been established for chronic bronchitis. However, relative to tetracycline dosage, it probably will require schedules of 0.9 to 1.8 gm. a day for acute exacerbations and 0.6 gm. a day for long-term therapy. The side reactions observed have been those seen with other tetracyclines. To date, photosensitivity reactions have not been noted in studies in which the patients were specifically challenged.

ACETYLCYSTEINE

The treatment of the troublesome secretions in chronic bronchitis has been significantly advanced with the introduction of acetylcysteine (N-acetyl-L-cysteine). This is a derivative of a naturally occurring amino acid, L-cysteine. In vitro acetylcysteine reduces the viscosity of

sputum, probably by action on mucoprotein through a specific sulfhydryl-disulfide interchange reaction which is concentration and pH dependent. The available form of acetylcysteine as the sodium salt also reduces the viscosity of solutions of deoxyribonucleic acid and hyaluronic acid owing to a nonspecific salt effect. Acetylcysteine is rapidly metabolized with the initial removal of the N-acetyl group and the subsequent catabolism following that of cysteine.[8] Unfortunately, very few of the in vitro studies have been carried out on freshly expectorated and physically and chemically unaltered human sputum. The activity of acetylcysteine is greatest with 10 per cent to 20 per cent solutions and at ranges of pH from 7 to 9. Acetylcysteine reacts irreversibly with most metals, with rubber, and, to some extent, with oxygen. Acetylcysteine has been used in a wide variety of clinical states with the common background of viscous tracheobronchial secretions, including chronic bronchitis. At the present time, its reported use has been in hospitalized patients and in those having the ancillary inhalation therapy equipment at home required for the administration of this agent. The clinical indication for its use in chronic bronchitis is the presence of obstructing secretions that are not being readily cleared from the tracheobronchial system with routine therapy. The most effective means of administration is by direct instillation into the tracheobronchial system through a tracheostomy, a bronchoscope, or a percutaneous intratracheal catheter. The recommended dose by direct instillation is 1 to 2 ml. of a 10 per cent to 20 per cent solution, although volumes up to 5 to 10 ml. can be used with caution. The dose can be repeated every hour if indicated. If cough does not clear out the secretions, then one should assist with the use of postural drainage, chest tapping, or gentle tracheal suction to remove the secretions within 15 to 30 minutes after administration of the agent. The administration of acetylcysteine has also been recommended as a nebulized inhalant. The dosage schedule for this means of administration is 1 to 10 ml. of the 10 per cent to 20 per cent solution nebulized through a face mask or mouthpiece every four to six hours. For use in oxygen, head, or croup tents, one may require 50 to 200 ml. to maintain a sufficiently heavy mist. At the present time, the use of acetylcysteine is recommended for short-term therapy in chronic bronchitis when simpler approaches have been inadequate. Long-term use has been reported to be useful in patients with cystic fibrosis, but comparative studies are not available in chronic bronchitis.

Actual toxicity to acetylcysteine is not expected with routine therapy. Sensitization has not been encountered. The most important side reaction is bronchospasm, which can be manifested very quickly in patients with bronchial asthma.[9] A degree of bronchial obstruction can also be noted in patients with nonasthmatic chronic obstructive lung disease.[10] When such bronchospasm occurs, it can be treated with an appropriate bronchodilator agent. This side reaction can be decreased or eliminated by the concomitant use of an aerosol bronchodilator (e.g., isoproterenol or racemic epinephrine) with the acetylcysteine. Nevertheless, acetylcysteine should be used with caution in asthmatic pa-

tients. Other side reactions have occasionally been noted and include nausea and vomiting, stomatitis, rhinorrhea, and rarely hemoptysis. If troublesome, the acetylcysteine should be discontinued. Caution should be exercised when administering acetylcysteine to insure that evacuation of the thinned secretion can be handled by the patient. Otherwise, measures for assisting the patient must be taken since the excessive secretions may drown a weakened patient.

The reports of the use of acetylcysteine in chronic bronchitis must be viewed with some caution because most studies are uncontrolled and measurements of the consistency of the freshly expectorated and untreated sputum are not usually carried out. Examination of the secretions raised is usually sketchy and the possibility that the reported acute increases of volume and decreases of thickness may be due to increased contamination of the specimen with saliva has not been excluded. Shaw et al.,[11] working with homogenized sputum specimens, were impressed by the mucolytic activity of acetylcysteine when it is instilled directly into the trachea in patients with acute and chronic respiratory diseases. Objective evaluation after administration of acetylcysteine by nebulization was not so clear, but the authors did note a decrease of sputum viscosity and an increase in sputum volume. Webb's initial experience with 285 patients included 14 with chronic bronchitis and emphysema.[12] The route of administration in these patients was not mentioned. He noted liquefaction of the secretion, increase of sputum volume, and easing of expectoration. No measurements of sputum volume or thickness are recorded. Later reports by Webb have been less specific about details. Reggiani et al.[13] used 3 per cent acetylcysteine with small concentrations of tetracycline by aerosol on a four day regimen. No controls were used. They found that viscosity as measured by the method of White and Elmes was decreased in 60 per cent of the patients, and most also noted ease of expectoration and increased volumes of sputum. Hirsh et al.,[14] in a controlled study using a more sophisticated means of measuring sputum consistency with a modification of the White and Elmes method, evaluated the acute effects of acetylcysteine and saline in patients with chronic bronchial disease. They used single nebulization treatments of 3.5 ml. of 20 per cent acetylcysteine or of normal saline. The sputum consistency decreased 73.3 per cent after acetylcysteine, compared to a 22 per cent decrease after saline in the 23 patients studied; this was a highly significant difference. In their experience, the patient's subjective evaluation of changes in ease of expectoration did not correlate with the changes of measured sputum consistency. In my experience this subjective symptom of ease of expectoration correlates with the stickiness or adhesiveness of the sputum, which is not measured by the principle of White and Elmes. In a subsequent work, Hirsch and Kory,[10] using the same methodology, reached the same conclusions but added that the 10 per cent solution was as effective as the 20 per cent solution. They noted a distinct tendency for acetylcysteine to result in an increase of bronchial obstruction as measured spirometrically. Although Hirsch

et al. froze and thawed their sputum specimens before studying them, the relative changes were probably not altered sufficiently to skew their results. In the most recent controlled study of Hirsch et al.,[15] ten patients with chronic bronchitis were treated with combinations of one or two of either acetylcysteine or saline and racemic epinephrine or saline for one week periods with crossovers during a total of seven weeks. They found that aerosolized acetylcysteine plus racemic epinephrine is effective in thinning sputum, whereas epinephrine alone tends to make sputum thicker. The combination seemed to prevent the increase of bronchial obstruction often noted with acetylcysteine alone.

In summary, acetylcysteine appears to be a useful mucolytic agent in treating the thick sputum of patients with chronic bronchitis. It is most effective when directly instilled into the tracheobronchial system, but recent reports indicate that it is also efficacious when administered by aerosol in patients with chronic bronchitis. It must be administered with care because of certain incompatibilities with rubber and metals, and caution must be exercised in asthmatic patients. Further studies will be required to determine its usefulness in routine outpatient home treatment.

BISOLVON

A new mucolytic, expectorant agent that is available in America only as an investigational drug, but that is in wide use in Europe, is worthy of brief discussion. N-cyclohexyl-N-methyl-(2 amino-3,5-dibromobenzyl) ammonium chloride is known as Bisolvon or NA274 and as such has been extensively studied in Europe. This drug can be taken orally, given parenterally, or aerosolized with significant mucolytic and expectorant effect. The mechanism of action appears to be the fragmentation of acid mucopolysaccharide fibers in the sputum with a resultant decrease of sputum viscosity. This has been demonstrated histochemically by Bürgi,[16, 17] who correlated his findings with viscosity measurements in vitro and in clinical studies. Guertler[18] demonstrated a significant increase of sputum volume in chronic bronchitis. He felt that optimal doses were probably around 32 to 40 mg. a day in divided doses. Guenthner[19] demonstrated an increase in pulmonary compliance, a decrease of respiratory work with an increase of low pO_2, and a decrease of elevated pCO_2. The effects noted in these studies have been repeatedly reconfirmed by other investigators. There are no reports of any significant toxicity, even after protracted oral use, and the side effects have been minor and infrequent. This agent is presently being investigated in America, and if it has only half the activity claimed for it in the European literature it will be an important addition to the treatment of chronic bronchitis. It is well tolerated orally and as effective as when given parenterally. In my intital studies with doses of 4 mg. four times a day, it was relatively inert. A present study is utilizing increased doses comparable to those used in Europe. The need for a nontoxic, effective mucolytic-expectorant that can be administered by various routes cannot be stressed too much.

The rationale for long-term antitussive therapy in chronic bronchitis has been confused by the lack of critical evaluation of the effects of such treatment. The ability to carry out such studies has been limited because of the lack of potentially effective non-narcotic antitussives until this decade. Our experience has been that a decrease of the severity and frequency of the often unphysiologic cough in chronic bronchitis is often helpful to the patient. Well designed studies of the effectiveness of antitussives in chronic bronchitis are difficult to find in the literature. This is reflected in the recommendations noted by the pharmaceutical firms in the information inserts in that chronic bronchitis is rarely given as an indication for use. Nevertheless, there is hardly any other group of patients who could note as much general improvement from the reduction of cough as those with chronic bronchitis. It is with apologies that the author discusses these newer non-narcotic antitussives which have, in general, been so inadequately studied with respect to their use in chronic bronchitis.

PIPAZETHATE

Pipazethate is chemically related to the phenothiazines. It is assumed that it acts centrally to suppress cough. In acute double-blind studies of acetylcholine aerosol-induced cough, 20 mg. was found by Prime[20] to be more effective an antitussive than 16 mg. of codeine. After oral administration, the onset of action occurs within 10 to 30 minutes and is effective for two to four hours. Its metabolic fate is unknown. Toxicity to this agent has not been described in man. Adverse side reactions are rare; they may consist of nausea, tachycardia, and urticaria. The usual recommended dosage schedule is 20 to 40 mg. four times a day. Occasionally, doses of 60 to 80 mg. four times a day have been used in our clinic with benefit. The indication for its use is troublesome chronic cough that is generally nonproductive of sputum and is causing insomia, fatigue, or other unwanted effects in the patient. Reports of the use of pipazethate in chronic bronchitis are few and poorly documented. Prime[20] reports the effective use of this agent in chronic bronchitis without any undesirable side effects. Gefter[21] found pipazethate to be effective in seven of eight patients with chronic bronchitis in an uncontrolled study. My experience has also been uncontrolled, but the general impression is that pipazethate is a fairly effective antitussive in chronic bronchitis when dosage is pushed to effective levels. When ineffective, it is at least nontoxic and unlikely to cause undesirable side effects.

CHLOPHEDIANOL HYDROCHLORIDE

Another antitussive, chlophedianol hydrochloride, is worthy of comment even though it was initially introduced in 1960. Chemically it is alpha-(2-dimethylaminoethyl)-chlorobenzhydrol hydrochloride and is related to the antihistamines. The onset of action is generally slower than that of other antitussives, but its duration of action is longer. The

indications for its use are the same as for pipazethate in chronic bronchitis. The recommended dosage of 25 mg. three or four times a day has often been found to be inadequate in the author's experience and daily doses up to 200 to 300 mg. have been used effectively. Although it is stated that the side effects are minor with the recommended doses, this has not been our experience. Hallucinations and syncope have been noted rarely with usual doses, but their occurrence is very troublesome in these instances. Other central nervous system symptoms of hyperexcitability or drowsiness have been reported, as have the more frequent gastrointestinal disturbances. Although these symptoms are seemingly more troublesome in chronic bronchitis than in diseases causing acute cough, the drug has been of use as an antitussive when the patients have been warned of the possible side effects and instructed to stop therapy at the start of such symptoms. The efficacy of this agent as compared to codeine has been confirmed in our laboratory in a double-blind crossover study and it actually had better acceptability than codeine.

GLYCERYL GUAIACOLATE

Although the title of this report implies that newer drugs in chronic bronchitis will be discussed, new information that provides a better understanding of older agents should be noted. Our laboratory has undertaken the evaluation of some such agents. Glyceryl guaiacolate, an expectorant agent that is widely used in simple syrup form or in combination with other agents used in pulmonary disease, was studied in a double-blind crossover study in patients with chronic bronchitis.[22] Besides subjective symptoms and physical examination, objective measurements of the stickiness and thickness of the sputum specimens were carried out, along with daily sputum volumes, pulmonary function studies, and other chemical and cytologic studies of the sputum. Studies in animals have previously indicated that glyceryl guaiacolate increases the volume of respiratory tract fluid and results in thinner secretions. Subjective studies in man have not confirmed this, but patients usually noted an easing of trouble in expectorating the sputum. In our study of 26 patients, the results indicated that although there was no change of sputum volume, the measured stickiness of the sputum decreased and correlated with those patients who noted a decreased difficulty in raising their sputum. This study was carried out with a dosage schedule of 100 mg. four times a day. Our clinical experience indicates that this was a very low dose and levels of 300 to 600 mg. four times a day have been used with more uniform subjective improvement. These results are noted here because of a notable reluctance of physicians to accept this useful expectorant as routine therapy in chronic bronchitis.

SULFADIMETHOXINE

In another study, the effectiveness of sulfadimethoxine used prophylactically to decrease or prevent acute exacerbations of chronic bronchitis was evaluated in a long-term winter study. This double-blind

crossover study was undertaken since sulfonamide drugs are commonly used for this purpose because they are less expensive than tetracyclines. In a randomized study each patient received for 16 weeks 1 gm. daily of sulfadimethoxine or placebo, and in the subsequent 16 weeks the alternate agent. Besides clinical, physiologic, and bacteriologic evaluations, the daily sputum volume and numbers of inflammatory cells in each daily sputum specimen were evaluated. The results of this study demonstrated that the sulfadimethoxine offered no prophylactic protection to the patient with chronic bronchitis against acute exacerbations and there was no difference in the level of sputum inflammatory cells. The sulfonamide did not cause any adverse results.

THEOPHYLLINE

It is also worth noting that a number of newer preparations of oral theophylline have become available that can provide effective blood levels. Oral maintenance therapy with this useful bronchodilator is now practical. Although all can cause gastric symptoms, they usually have better acceptability than some of the older oral aminophylline preparations. Of the more commonly known of these preparations, only Elixophyllin contains no other active agent, but is made up in 20 per cent alcohol. Quibron and Brondecon both have guaicol derivatives combined with the theophylline. These agents have provided an important mode of theophylline therapy in readily accepted dosage forms, and for this reason should be mentioned under newer drugs.

PROTEOLYTIC ENZYMES

Over the last few years, the previously acceptable proteolytic enzymes given by the oral route of administration have fallen into disuse. The lack of controlled and well documented studies to support claims for anti-inflammatory activity of these oral proteolytic enzymes appears to have reduced the enthusiasm for their use. There is only minimal evidence that these agents offer any mucolytic activity in chronic bronchitis. It may be of interest that in a limited double-blind study of buccal alpha amylase, a starch-splitting enzyme used in doses of 10 to 20 mg. four times a day, there was a decrease in the thickness of the sputum in nine of ten patients. It should be emphasized that our results have not been subjected to further analysis because of the paucity of data to support its anti-inflammatory actions. These comments are offered to point out that most of these agents have fallen into disuse without ever having been properly evaluated in chronic bronchitis.

SUMMARY

In conclusion, there have been a few worthwhile new drugs for the treatment of various aspects of chronic bronchitis. Of those discussed, two have particular merit. Ampicillin appears to be an effective agent in treating the bacterial aspects of chronic bronchitis and may become the drug of choice in this area. Acetylcysteine has provided the first

worthwhile mycolytic agent that can be used directly in the tracheobronchial system. With the increased interest in this very common disease, the ability to treat early cases effectively, as well as the more severely ill patients, becomes more important. Despite the poor understanding of the etiology and pathogenesis of chronic bronchitis, it is through such therapeutic agents – as well as more definitive preventive measures – that there can be hope of decreasing the alarming morbidity and mortality attributed to chronic bronchitis in this country and in the rest of the world.

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Effective Antifungal Drugs and Indications for Their Use

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During the past 10 years many chemotherapeutic agents have been developed for the management of superficial and deep fungus infections. Some of these, such as amphotericin, nystatin, and griseofulvin, are antibiotics; others, like tolnaftate and hydroxystilbamidine, are complex chemical compounds. Most of these drugs have selective specific action against certain individual superficial or deep fungus infections. Prior to the introduction of griseofulvin for the systemic treatment of superficial mycotic infections, physicians were dependent on relatively ineffective topical preparations containing keratolytic agents (benzoic acid, salicylic acid, or the salts of undecylenic acid and propionic acid) as the active ingredients.

It must be emphasized that these antifungal drugs are specifically intended for the management of mycotic infections and are of no value in the treatment of other conditions. The failure of other dermatoses to respond to administration of these compounds has been repeatedly demonstrated. The similarity in clinical appearance of cutaneous fungus infections and other dermatoses makes the laboratory diagnosis essential. The presence of fungi must be established by direct microscopic examination before therapy is initiated with these new remedies. The causative organism must be demonstrated by culture.

Although specific agents have been developed for the treatment of many of the deep fungus infections, the saturated solution of potassium iodide is still the drug of choice in the treatment of sporotrichosis. Penicillin is the most effective agent in the treatment of actinomycosis and the sulfonamides are preferred in the treatment of nocardiosis.

TOPICAL THERAPY

The preparations described in the following paragraphs are the only effective topical fungistatic or fungicidal drugs commercially available for human use. Preparations containing the salts of undecylenic acid or

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propionic acid depend on keratolytic activity for therapeutic value and are inferior to tolnaftate, nystatin, and amphotericin B in producing satisfactory subjective and objective improvement.

Tolnaftate

Tolnaftate (O-2-naphthyl m,N-dimethylthiocarbanilate), synthesized in 1960, is the first chemical compound to have specific fungicidal activity on topical application. It is a colorless, odorless compound that is soluble in most organic solvents and insoluble in water. In vitro studies indicate that tolnaftate has the ability to distort hyphae and stunt the mycelial growth of susceptible species.[1] Quantitative studies using the agar dilution test method showed that tolnaftate in a concentration of 0.075 μg./ml. is fungistatic against Trichophyton mentagrophytes and at 0.0075 μg./ml. by the tube dilution method. The fungicidal level was 0.75 μg./ml. by the agar dilution method and 0.075 μg./ml. by the tube dilution method. In vitro studies also proved that tolnaftate is ineffective against Candida albicans and gram positive and gram negative bacteria.

Oral and parenteral administrations of tolnaftate were ineffective in the treatment of guinea pigs inoculated with mycotic infections. However, when these same pigs were treated with the drug applied topically, involution of lesions and negative cultures developed within 7 to 9 days. In vitro studies indicate that tolnaftate has antifungal activity against infections produced by Microsporum gypseum, Trichophyton rubrum, Microsporum canis, Epidermophyton floccosum, Trichophyton tonsurans, Microsporum audouini, and Trichophyton mentagrophytes. Clinical trials proved it to be effective in the treatment of tinea versicolor. Cutaneous monilial infections were not benefited.

CLINICAL INDICATIONS. One per cent solution of tolnaftate in polyethylene glycol or a vanishing cream base proved to be an effective agent for the treatment of superficial mycotic infections due to Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Trichophyton tonsurans, and Microsporum audouini. Lesions on the trunk and in the groins involuted in 10 to 14 days. Lesions on the scalp due to Trichophyton tonsurans and Microsporum audouini did not respond to this topical medication. Lesions due to Candida albicans did not respond. Satisfactory results were not obtained in the treatment of onychomycosis. In all conditions in which itching was a prominent symptom, there was relief in 24 to 72 hours regardless of the duration of the eruption. Involution of interdigital lesions due to the previously mentioned susceptible fungi was complete in 7 to 21 days. This result could not be accomplished by the use of systemically administered griseofulvin or topically applied keratolytic agents. Tolnaftate solution is effective in the treatment of tinea versicolor.

One per cent solution of tolnaftate in polyethylene glycol or in a vanishing cream base is to be applied topically to the involved areas twice daily. It is usually necessary to use 10 per cent salicylic acid ointment or Whitfield's ointment alternately with the tolnaftate preparation in the treatment of hyperkeratotic palmar or plantar infections.

Toxic Effect. Adverse reactions to the topical application of tolnaftate were not encountered. In massive doses, administered to dogs, the drug did not produce toxic effects. Doses of 0.5 gm./kg. daily for 30 consecutive days did not produce abnormalities in external appearance or body weight and there were no gross or microscopic pathologic changes observed at autopsy.

Evaluation of Results. Tolnaftate in one per cent solution or cream applied topically proved to be an effective antifungal agent in the treatment of eruptions due to Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, Microsporum canis, Microsporum audouini, Microsporum gypseum, and Malassezia furfur. Evidence of primary irritation or acquired contact sensitivity was not encountered in a series of 323 patients. The preparation has proved to be ineffective in the treatment of eruptions due to Candida albicans or lesions in the scalp or nails due to the dermatophytes. The relapse rate in patients treated with tolnaftate approximates the rate obtained with those treated with griseofulvin. Evidence of resistance did not occur and patients responded to retreatment with the topical compound. Establishment of the diagnosis by laboratory methods is essential.

Acrisorcin (Akrinol)

Acrisorcin (9-aminoacridine salt with 4-hexylresorcinol; 9-aminoacridinium 4-hexylresorcinolate) is an antifungal agent whose sole value is in the treatment of tinea versicolor. It is a colorless, odorless compound dispensed for clinical use in 0.2 per cent concentration in a vanishing cream base. The effectiveness of this substance in the treatment of tinea versicolor was determined by clinical experimentation alone because suitable laboratory methods for its evaluation have not been developed.[2] The use of Akrinol should be restricted to the treatment of tinea versicolor because it is not effective in the treatment of any other cutaneous infection.

Dosage. The 0.2 per cent acrisorcin cream is applied to the involved areas twice each day. Patients should be instructed to take a shower with copious amounts of soap and water each morning and evening, rinse thoroughly, pat the skin dry, and then apply the medication. Treatment should be continued for at least 4 weeks after direct microscopic examinations from the lesions are negative for Malassezia furfur.

Evaluation of Results. The difficulties of performing an adequately controlled study in the treatment of tinea versicolor are apparent. The condition itself is chronic and prone to relapse. Experience has indicated that relapses do respond to re-treatment with acrisorcin. The drug is not as effective as tolnaftate solution or cream.

Nystatin (Mycostatin)

Nystatin, $C_{46}H_{77}NO_{19}$, is a pale yellow, water-insoluble, almost odorless substance. It is an antibiotic extracted from Streptomyces noursei and has specific action against Candida albicans. The drug is of no value in the treatment of any other type of infection. It is poorly ab-

sorbed from the gastrointestinal tract and even after administration of exceptionally large doses the blood level is insignificant.

CLINICAL INDICATION. Nystatin is effective in the treatment of localized candida infections in the vagina, on the skin, and in the mouth. It may be used in conjunction with broad spectrum antibiotics to prevent intestinal monilial infection. The superficial monilial infections that commonly occur in the groin, vagina, and mouth, at the angles of the mouth, between the fingers, and in the nail folds respond to topical therapy with Mycostatin when dispensed in a suitable medium. Nail involvement due to Candida albicans is not benefited.

DOSAGE. A combination of Mycostatin with neomycin and a steroid prepared in a vanishing cream or ointment base is effective in the treatment of perlèche (angular cheilitis) and Candida albicans infections of the groins or anal area.

Monilial infection of the vagina will respond to the insertion of vaginal tablets (100,000 units) twice daily for a minimum period of 2 weeks. It may be necessary to repeat this treatment for relapses. Evidence of resistance to the drug has not been encountered. In the treatment of thrush (monilial oral infection), Mycostatin powder is an aqueous suspension containing 100,000 units of nystatin per cubic centimeter, is administered orally. Patients are instructed to take approximately 2 cc. in the mouth and hold it for a prolonged period before swallowing. This same procedure is to be repeated three or four times daily. Treatment should be continued for a prolonged period after all clinical lesions have subsided.

The coated tablets of nystatin, each of which contains 500,000 units, are effective in the treatment of intestinal monilial infection. The patient should be given four 500,000 unit tablets daily in divided doses. If given concurrently with a bacterial antibiotic, the Mycostatin must be administered over the same period of time as the other drug.

Monilial infection of the lungs, liver, and other organs responds poorly to systemic nystatin primarily because of poor absorption from the gastrointestinal tract.

Selenium Sulfide

Selenium sulfide detergent suspension (2.5 per cent) and the 0.5 per cent ointment have been recommended as a topical treatment for seborrheic dermatitis. Robinson and Yaffe[3] found that selenium sulfide is of value in the treatment of tinea versicolor. Their original study was conducted using the 0.5 per cent selenium sulfide ointment but more recently the suspension has also been found effective.

CLINICAL INDICATION. The clinical appearance of tinea versicolor is characteristic. It is simple to prove the diagnosis by direct microscopic examination. Cultural methods are not uniformly satisfactory.

The patient should take a shower with warm water and soap, rinse thoroughly, and pat the skin dry. The ointment is applied without rubbing twice each day. When the selenium sulfide suspension is used, it is applied to the wet skin immediately after the shower and the skin is

gently massaged until a lather forms. This is allowed to dry. Treatment should be performed daily for at least one week after all lesions have become quiescent and the direct microscopic examinations are negative.

Adverse Reactions. Selenium sulfide has a low index of sensitization. The preparation should not be used on any area where there is any evidence of acute inflammation. Patients should be instructed to wash the hands thoroughly and clean beneath fingernails to remove all traces of the drug after each application. If ingested, selenium sulfide is a very toxic substance.

This drug has proved to be effective in the treatment of tinea versicolor. Evidence of resistance has not developed and relapses have responded to re-treatment with the same preparation.

Amphotericin B Lotion

This is an antifungal antibiotic derived from a strain of Streptomyces nodosus. The amphotericin B lotion (Fungizone) has great activity against Candida albicans and is a superior method of treatment of cutaneous and mucocutaneous monilial infections. This includes inframammary, groin, interdigital, and oral lesions. It is especially effective in the treatment of monilial infections of the diaper area. Fungizone is not active against lesions produced by the superficial dermatophytes.

Amphotericin B lotion contains 3 per cent of the active ingredient in an aqueous lotion vehicle. When used in the treatment of lesions under the breasts, in the axillae or groins, about the anus, in the interdigital spaces, and about the fingernails, the lotion is to be applied two or three times daily. Response to treatment is usually prompt. Lesions subside completely in a week to 10 days. Applications should be continued for at least one week after all signs and symptoms have disappeared. The lesions between the fingers may require more prolonged therapy. Treatment of toenail lesions has been unsatisfactory.

Toxic Effect. There has been no evidence of systemic toxicity from topical application of this material. The sensitizing potential is very low.

SYSTEMIC ANTIFUNGAL THERAPY

Griseofulvin, amphotericin B, and hydroxystilbamidine isethionate are effective on systemic administration in the treatment of most of the superficial dermatophytes and deep fungi, the exceptions being sporotrichosis, actinomycosis, and nocardiosis.

Saturated solution of potassium iodide administered orally is the drug of choice in the treatment of sporotrichosis. Therapy is initiated with a dose of 10 drops three times daily in one fourth glass of water. This dose is increased by one drop per dose per day until the patient is receiving 60 drops of saturated solution of potassium iodide three times each day. This large dose may cause nausea and vomiting. Long-continued administration of potassium iodide frequently causes severe folliculitis or cutaneous granuloma formation.

Penicillin is by far the most effective drug used for the treatment of actinomycosis. The antibiotic should be given by injection, using one of the long-acting preparations so that the patient may receive the large quantity in each daily dose necessary for satisfactory result. A minimum dose of 1.2 million units should be given each 24 hours and continued for at least 3 weeks after all signs and symptoms of the condition have disappeared.

Sulfonamides are the drugs of choice in the treatment of nocardiosis. Sulfadiazine in a dose of 6 to 8 gm. daily should be given until all objective signs of the disease have disappeared. Administration of the drug should be continued for at least 2 weeks after healing is complete. Some of the nocardia species are susceptible to the broad spectrum antibiotics. It may be desirable to use a combination of a broad spectrum antibiotic with the sulfonamide of choice.

Griseofulvin

Griseofulvin (7-chloro-2′,4,6-trimethoxy-6′-methylspiro-(benzofuran-2(3H),1′-(2)-cyclohexene)-3,4′-dione) is an antifungal antibiotic isolated from Penicillium griseofulvum. This is the first chemical compound proved to be effective on oral administration in the treatment of infections due to the superficial dermatophytes.[4] It is an odorless, white, thermostable substance that has some cytotoxic properties similar to those of colchicine. It is relatively insoluble in water and olive oil but is soluble in ethyl alcohol, Carbowax 300, chloroform, acetone, and butylacetate. In vitro studies proved this drug to be fungistatic against Trichophyton rubrum, T. tonsurans, T. mentagrophytes, T. verrucosum, T. sulfureum, T. schoenleini, Microsporum audouini, M. canis, M. gypseum, and Epidermophyton flocossum. It is not effective against bacteria, Candida albicans, or any of the deep fungi.

CLINICAL INDICATIONS. Griseofulvin is effective in the treatment of tinea capitis, tinea corporis, onychomycosis, and tinea cruris. Results are disappointing when the drug is used in the treatment of interdigital infections due to the dermatophytes. It is of no value in the treatment of tinea versicolor or monilial infections.

In the treatment of tinea capitis due to Microsporum audouini, M. canis, or Trichophyton tonsurans, a single massive dose of 3 gm. of the large particle griseofulvin or 1.5 gm. of the micronized griseofulvin will produce a satisfactory result in about 80 per cent of the patients. A satisfactory result is not obtained until 4 to 5 weeks after therapy is initiated. The patient should be observed periodically under the Wood light until fluorescence has completely disappeared. A negative culture from the involved area is final evidence of cure. If the continuous form of therapy is used in place of the massive dose technique, the patient is to receive 1 gm. of the large particle griseofulvin or 0.5 gm. of the micronized griseofulvin in divided doses daily for 4 to 5 weeks.

Massive dose therapy of griseofulvin is of no value in the treatment of tinea corporis or tinea cruris. Oral therapy with griseofulvin using the large particle (1 gm. per day) or the micronized form (0.5 gm. per day) must be administered daily in divided doses over a period of 4 to 5

weeks. Treatment of onychomycosis with these drugs is of great value but the daily dose must be administered continuously without a rest period for 4 to 6 months. Fingernail involvement usually has an excellent response to treatment but toenail infections have a poor prognosis.

Adverse Reactions. Epigastric discomfort, nausea, and diarrhea are the most commonly encountered side effects of oral administration of griseofulvin. Photosensitivity reaction and urticaria are occasionally observed. Patients under griseofulvin therapy should avoid unnecessary exposure to sunlight. Serious adverse reactions have not been encountered.

Evaluation of Results. In vitro and in vivo studies have failed to develop evidence that susceptible species will develop resistance to this antibiotic. Patients who have suffered relapses after successful treatment with griseofulvin have responded to retreatment.

Amphotericin

This is an antifungal antibiotic derived from Streptomyces nodosus. It is a yellowish powder that is relatively insoluble in water. For intravenous use it is prepared as a sterile lyophilized powder and it is dispensed in vials containing 50 mg. of amphotericin B and approximately 41 mg. of sodium desoxycholate with 10 mg. of dibasic sodium phosphate and 0.89 mg. of monobasic sodium phosphate added as buffers and 6.2 mg. sodium chloride. The drug has fungistatic action against Coccidioides immitis, Histoplasma capsulatum, Candida albicans, Cryptococcus neoformans, Blastomyces dermatitidis, and Blastomyces brasiliensis. The antibiotic is not active against bacteria, protozoa, or viruses. The therapeutic effect of this drug is probably due to the fact that it interferes with a critical metabolic pathway in intact yeast cells. It is poorly absorbed from the gastrointestinal tract therefore in order to exert its action it must be injected intravenously.

Clinical Indications. This drug is specifically intended for the treatment of deep mycotic infections including coccidioidomycosis, cryptococcosis, systemic moniliasis, histoplasmosis, South American leishmaniasis, and North and South American blastomycosis. Patients to be treated with this drug should be hospitalized.

The preparation for intravenous administration must be carefully supervised. The recommended concentration is 0.1 mg./cc., which is obtained by first dissolving 50 mg. of amphotericin B powder in 10 cc. of sterile water and agitating this until clear. This is further diluted with 5 per cent dextrose solution to provide a concentration of 0.1 mg. of amphotericin B per cubic centimeter.

Therapy should be initiated with a daily dose of 0.25 mg./kg. of body weight and gradually increased until the optimum level is obtained. It may be possible to reach the level of 1 mg./kg. of body weight provided that serious adverse reactions do not develop. For seriously ill patients, not benefited by this amount, it may be possible to increase the daily dose gradually to 1.5 mg./kg. provided there is no evidence of renal failure. After improvement is evident it is usually possible to reduce the

drug administration to every other day. The usual course of therapy lasts from 6 to 8 weeks. If treatment is discontinued too soon, there may be a relapse.

ADVERSE REACTIONS. Amphotericin B is a nephrotoxic drug and therefore the blood urea nitrogen level and other kidney function tests must be checked regularly during the course of treatment. The chief toxic effects are nausea, vomiting, fever, loss of appetite, hematuria, and albuminuria. If evidence of kidney damage develops, it usually subsides when the medication is discontinued.

This is an effective preparation but is must be remembered that it is fungistatic and not fungicidal; therefore, treatment should be continued until all signs and symptoms of the disease have disappeared.

Hydroxystilbamidine Isethionate

This drug, a yellow crystalline powder, is stable in air but decomposes on exposure to light. This compound has been found effective in the treatment of North American blastomycosis, leishmaniasis and African trypanosomiasis. It is of no value in the treatment of torulosis or histoplasmosis.

CLINICAL INDICATION. In the treatment of blastomycosis, for which it is specifically indicated, the dose is 150 mg. daily, diluted with 200 cc. of 5 per cent dextrose solution administered as a slow intravenous drip. Treatment must be given daily for a period of 8 to 10 weeks, depending on the extent of the condition and response of the patient. The preparation for injection must be carefully supervised. The solution will decompose and form toxic products when exposed to heat, sunlight, or ultraviolet radiation. Patients who are under treatment with this drug must avoid exposure to direct sunlight during the course of therapy.

ADVERSE REACTIONS. Immediately following injection of the drug the patient may experience a fall in blood pressure with tachycardia, flushing of the skin, sweating, nausea, vomiting, dizziness, shortness of breath, and fainting. Trigeminal neuropathy may also develop.

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Newer Steroids in Nonviral Encephalitis

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Only in a few forms of encephalitis has the therapeutic place of adrenal cortical steroids or of corticotropin been firmly established. In other entities their usefulness appears probable, while in still others, there is little evidence that they are indicated. The major problem in reviewing this field is the impossibility of identifying the etiology of many cases of clinical encephalitis, and the resulting confusion in identifying homogeneous groups of cases.

Many cases of viral encephalitis can readily be identified by the clinical picture: the abrupt onset of fever, disturbances in state of consciousness, seizures and migratory neurological signs. The spinal fluid characteristically shows pleocytosis. This syndrome is particularly easy of recognition in summer, when the arthropod-borne encephalitides are prevalent and frequently epidemic, and when upper respiratory virus infections are less common. The pathological lesion is one of perivascular cuffing of cerebral vessels and neuronal changes. The virus is frequently present in the cerebrospinal fluid. The place of adrenal cortical steroids in the treatment of viral encephalitis is controversial,[8] but the case group is fairly well defined.

Apparently quite a different syndrome is the encephalopathy following, for example, the administration of Semple rabies vaccine. After an interval of several days following the injection of a presumably dead or inactivated viral substance the patient develops a neurological illness, frequently with prominent signs of involvement of the spinal cord, optic nerves, brain stem and cerebral hemispheres. This illness may or may not be accompanied by fever and pleocytosis. It may serve here as the prototype of a group of illnesses thought to be noninfectious in nature. They include the postexanthematous encephalitides, postvaccinial encephalitis, post-Semple vaccine encephalitis and acute disseminated encephalomyelitis occurring after a variety of known or suspected viral

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infections, or with no known preceding illness. Some of these cases are followed by the life history of multiple sclerosis.[9, 78]

It is this latter group of illnesses with which this review is concerned; their clinical features have been extensively studied, and also their pathology. There are early perivascular cellular cuffing, inflammatory changes in vessel walls and perivenous demyelination, particularly in the white matter of the central nervous system. These illnesses have long been recognized as similar in their clinical features and pathological lesions to the encephalomyelitis so readily produced in numerous species of animals by injection of different preparations made of brain and spinal cord and, in recent years, of a purified basic protein fraction thereof – so-called experimental allergic encephalomyelitis (EAE). For many reasons, this experimental encephalomyelitis, which can now be transferred from one animal to another by lymph node transfer, has been thought to be a disease of autoimmunity, the injected substance causing the organism to produce an immune response to its own nervous tissue.[64] These experimental illnesses can be suppressed by the use of adrenal cortical steroids, a phenomenon that is discussed more fully later.

The clinical distinction, however, between viral infection and postinfectious or disseminated encephalomyelitis is frequently most difficult.[62, 73] An illness characterized by premonitory symptoms of malaise and upper respiratory infection, followed by central nervous system disease, may clinically closely resemble acute disseminated encephalomyelitis (ADE) yet be due to a virus.[46] Conversely, the clinical and spinal fluid picture of acute viral encephalitis can be duplicated exactly by illnesses in which no virus is demonstrated, and in which the pathological findings are those of ADE.[57] Inclusion bodies have recently been reported in brain from measles encephalitis, suggesting that this disease, which has been thought to be neuroallergic (and by extension other "postexanthematous" encephalomyelitides), may be due to a direct virus invasion.

The lack of a clear clinical distinction between viral infection of the nervous system and postinfectious, or nonviral, disease prevents a convincing evaluation of adrenal cortical steroids on a homogeneous group of cases.

EFFICACY OF ADRENAL CORTICAL STEROIDS IN SPECIFIC ENTITIES

Measles

The role of steroids in the treatment of measles encephalitis is particularly obscure at the present time, since Adams et al. recently reported that 15 of 20 fatal cases showed the "hallmark of the measles virus, typical cytoplasmic or nuclear inclusion bodies, or both. . . ." These authors make a strong case for measles encephalitis frequently being due to a direct viral involvement of the nervous system, although only two reports have been made of an isolation of the measles virus from brain or CSF of patients with measles encephalitis.[2]

The use of steroids has been commented on in several large series of measles encephalopathy. Boughton, in a series of 170 patients, stated that he could not assess the usefulness of steroids from his study.[11] Allen, using a combined regimen of hydrocortisone, corticotropin and antibiotics in 10 patients, reported complete, usually dramatically sudden, recovery in all 10. He contrasted this with an increased mortality and morbidity of previously reported cases treated either with supportive measures only or with gamma globulin.[4] Two subsequent studies, however, have cast doubt on the efficacy of steroid treatment. Karelitz and Eisenberg reported the same incidence of neurological sequelae in a group of measles encephalitis patients treated with ACTH as in a control group and doubted the efficacy of the agent.[41] Ziegra, in another controlled study, using the same regimen as that of Allen, found no benefit either in mortality, length of illness or sequelae.[85] Meade states, from personal observation of 50 patients who recovered quickly from severe encephalitis without use of steroids, that he feels the value of the agents has yet to be established.[54]

Although the literature is controversial, Koprowski stresses the point that if measles encephalitis is due to a hyperergic mechanism and can be analogized to EAE, a fair test of the use of steroids would be its use during the period of sensitization to the antigen.[47]

Varicella

The use of adrenal cortical steroids or ACTH has been little studied in the neurological complications of varicella. In the case of Jenkins[38] the patient was given dexamethazone along with many other therapeutic agents. The child recovered, but the role of dexamethazone was unclear.

The use of adrenal cortical steroids in varicella encephalitis is particularly controversial because their use has been associated with the transformation of a benign varicella infection to the severe disseminated disease with death and hemorrhagic virus-infected vesicles throughout the viscera.[33] The case of acute fatal encephalitis occurring in a child who developed varicella while receiving cortisone for asthma is of particular note. Whether steroids being administered for other reasons should be discontinued or reduced in amount in a child developing varicella is currently a matter of controversy.[1, 18, 22] It is of interest that despite the well known action of the steroids in diminishing the physiological reactions to, and defenses against, infection, there is little clinical data, except this on varicella, to indicate adverse effects on viral infections in man. Live viruses have been inoculated into cortisone-treated patients with malignant disease with the intent to damage or destroy the neoplasms, yet the numbers and severity of the infections were only slightly higher than in controls.[76]

Rabies Vaccine Encephalomyelitis

Among the most striking and consistently favorable reports of the use of ACTH or adrenal cortical steroids are those in cases of neurological complications of the use of the Semple rabies vaccine.

This group of phenomena is of special interest for several reasons. The disease states, which are clinically and pathologically similar to the neurological diseases following the exanthematous and other viral diseases, are clearly induced by the injection of viral particles, presumably dead or inactivated, and therefore acting as an antigen. They are, therefore, of all clinical syndromes, the most analogous to EAE.[63] These cases are also of interest because some of those occurring in Japan have had a prolonged subacute course, and the demyelinating lesions seen at autopsy have been similar to those of multiple sclerosis.[81]

Although no controlled series have been studied, because the condition is rare, at least four case reports record an extremely rapid reversal of severe neurological dysfunction following the use of adrenal cortical steroids.[6, 13, 30] There is no record, however, of results of steroid treatment of the large number of cases in the Japanese series.

The preceding discussion applies also to the rare neurological complications of vaccination for smallpox. Rapid reversal of neurological signs and symptoms has also occurred in this clinical situation following the use of cortisone and ACTH.[60]

Acute Disseminated Encephalomyelitis of Other Cause

Cases of neurological disease indistinguishable from those previously discussed occur following rubella, pertussis, scarlatina,[57] influenza,[23, 53, 77] infectious mononucleosis[21, 25] and numerous other proved viral diseases.[14, 46] Acute disseminated encephalomyelitis also occurs after nonspecific upper respiratory disease, and with no known antecedent infections. Controlled studies of the value of adrenal cortical steroids or ACTH have not been done in these cases, but there are many reports of their rapid efficacy in individual cases and series of cases.[40, 56, 74, 84] Representative of this group is the following case:

A 3½ year old boy was given antibiotic and antitussive agents for an illness diagnosed as a common cold, and one week later became ataxic, nauseated and lethargic. Within a matter of hours after admission to the hospital the child developed dilated, poorly reactive pupils, blurred optic disks and blindness. There were also bilateral Babinski signs, left hemiparesis and nuchal rigidity. A ventriculogram was done, and the ventricular fluid contained 100 WBC (84 per cent mononuclear cells) and a protein of 66 mg. per 100 ml. Intramuscular prednisone was begun, and vision returned in 36 hours, with disappearance of other neurological signs over the next four days. The child was asymptomatic by the seventh hospital day, but the spinal fluid contained 15 WBC and 50 mg. of protein.

The child was discharged from the hospital and prednisone administration was stopped, but within four days blindness, ataxia, bilateral Babinski signs and choreiform movements again developed. Spinal fluid pressure was 580 mm. H_2O, but the cerebrospinal fluid was otherwise normal. Prednisone, 10 mg. three times daily, was reinstituted, and the child again rapidly recovered. Prednisone was continued for two weeks and then gradually discontinued. Two years after the illness the child was subject to occasional psychomotor and focal motor seizures, and also recurrent episodes strongly suggestive of multiple sclerosis.*

*This case is reported at greater length in Arch. Neurol. *14*:476, 1966.

Miller, whose experience in this field is probably unsurpassed, stated in 1961 that, although he had treated 40 patients with this condition and documented many examples of dramatic reversal of signs and symptoms such as those reported in the case just described, he could not be sure they were not coincidental.[56]

POSSIBLE STEROID EFFECT ON PATHOPHYSIOLOGICAL MECHANISMS IN ENCEPHALITIS

The continuing uncertainty as to the effectiveness of the steroids in encephalitis may stem from the fact that these agents have different physiological actions, which may be of specific benefit only in those certain cases to which they are applicable. The number of such cases may be small enough to be difficult of detection in small series. In the following paragraphs the possible mechanisms by which the steroids might be of benefit in different illnesses are discussed.

Cerebral Edema

Patients with all types of acute encephalopathy frequently show increased spinal fluid pressures and increased intracranial pressure, notably papilledema. At autopsy pressure cones at the tentorium cerebelli and at the foramen magnum are common.[32, 52] The brain in all kinds of acute encephalitis is frequently heavy and moist and shows microscopic evidence of cerebral edema.[32] Evidence of cerebral edema also is frequently present, specifically in the "postinfectious" encephalitides of the exanthemata and following other infections,[57] and is a feature of the pathology of the experimental allergic encephalomyelitis.[44]

Much is unknown about the etiology of cerebral edema, but it is reasonable to assume that the perivascular lymphocytic cuffing and dilatation of small blood vessels seen on microscopy in encephalitis is evidence for an abnormality of the vascular wall, with increased permeability and escape of fluid into adjacent tissues. (Lyon et al., however, believe that the edema shown in the brains from patients with "toxic encephalopathy" may be secondary to cerebral anoxia suffered by patients as a result, for example, of airway obstruction and impaired ventilation.[52])

It is well known that both the adrenal cortical steroids and ACTH increase vascular tone and suppress the vasodilatation that occurs from various kinds of noxious agents. Exudation of fluid and cells is greatly reduced. Increased vascular tone and decreased capillary permeability have been observed directly in the rabbit ear chamber and in the cornea of man.[15, 31]

That adrenal cortical steroids are effective in clinical situations of cerebral edema without encephalitis has been abundantly documented. Most work has been done on the cerebral edema associated with brain tumors, particularly the gliomas, although favorable results have occurred with all kinds of intracranial neoplasia.[27, 29, 71]

The increased intracranial pressure secondary to head trauma,[37] subarachnoid hemorrhage[24] and intracranial surgery[68] has also been successfully treated with adrenal cortical steroids. It has been demonstrated that these agents lower ventricular pressure[48] and produce remarkable temporary improvement in these varied clinical situations presumably ascribable to the reduction of edema.

The adrenal cortical steroids may also be of use in combating the cerebral edema frequently associated with cerebral infarction, although the evidence is controversial. That marked swelling of the brain occurs following ischemic infarction is well known.[75] Plum et al. found no therapeutic effects of steroids on rats with experimental cerebral infarction.[66] In man, Dyken and White found no therapeutic effect in one double blind study,[17] while Rubinstein, confirming earlier studies,[69, 72] found the steroids of use with the important proviso that their usefulness was limited to the very early period of infarction, before herniation of the uncus or the cerebellar tonsils, and in the absence of brain stem dysfunction.[70]

Swelling of the brain can also occur in episodes of demyelinating disease, undoubtedly due to cerebral edema.[67]

The mechanism by which steroids reduce cerebral edema in these situations is unknown; they do not shrink the brain by dehydrating the tissues. There is much evidence that their effect depends on the alteration of cerebral electrolyte distribution, particularly in the white matter.[5, 51]

It is reasonable to assume that the adrenal cortical steroids would be useful in combating the cerebral edema due to encephalitis by antagonizing the vasodilation, preserving the integrity of vascular walls and preventing the escape of fluid into brain tissue.

This therapeutic mechanism theoretically would be operative in the acute phase of the encephalitides, in the presence of increased intracranial pressure. Several authors reporting favorable effects of steroids in cases of trichinella encephalitis,[16] polioencephalitis[36] and postexanthematous encephalitides[12, 61] have stressed that the agents were effective only in the first few days of the illness and that the response was frequently abrupt and most easily explained by reversal of cerebral edema.

The large retrospective study of Bøe et al., however, on use of corticosteroids in acute meningoencephalitis of all kinds, did not confirm this therapeutic effect, nor did they find evidence of therapeutic effect even when those patients admitted in coma (presumably most likely to have cerebral edema) were selectively studied.[8]

The adrenal cortical steroids have proved effective also in combating and preventing experimental cerebral edema produced by intracerebral, extradural or subdural implantation of psyllium seeds[50, 51] or by injection of vegetable oil into the carotid artery.[7]

Recent light and electron microscope studies have shown that cerebral edema is a most heterogeneous entity; the type associated with infectious or noninfectious encephalitis may or may not be similar to

some of the kinds of cerebral edema experimentally produced or occurring with cerebral trauma or tumors. Some types of edema affect principally white matter, others gray matter. Klatzo, in a recent review, categorized cerebral edema into two major types: vasogenic, in which the disturbance is probably in the walls of the blood vessels (in areas adjacent to neoplasia or trauma), with the observation that one could postulate a known steroid effect on the vascular wall to explain a therapeutic effect on this edema in this type; and cytotoxic, in which, for unknown reasons, intracellular, protein-poor fluid, which is an ultrafiltrate of the plasma, accumulates. Steroids would be less likely to combat this phenomenon.[45]

That massive cerebral edema occurs in many acute cases of these encephalitides is undoubtedly true, but it is unknown whether this is vasogenic or cytotoxic in nature or both. It is possible that the success of steroids in some cases occurs because of prominence of "vasogenic" edema, their failure in others because morbidity is due to "cytotoxic" edema. There are no data on the effect of steroids on spinal fluid pressures, nor on any measured clinical phenomena in ADE patients; there are only the many clinical reports of their success.

Alteration in the Immune Response

The leading hypothesis as to etiology of the postexanthematous and postinfectious encephalomyelitides has been, as discussed previously, that of a hyperergic or allergic reaction of the nervous system. It has also been previously mentioned that there are many points of similarity, both clinical and pathological, in the clinical diseases to the experimental allergic encephalomyelitis. The use of adrenal cortical steroids or corticotropin could then be of use in the clinical syndromes to suppress the immune process itself. If this were the mechanism of therapeusis of these agents, the timing of the administration of drugs, and possibly their dosage, would be critical.

It has long been known that cortisone and corticotropin exert definite suppressive effects on experimental encephalomyelitis in various species. Results have varied from partial to total suppression of the disease in guinea pigs[20, 59] and in monkeys,[19, 39] provided the agents were given either before the antigenic challenge or very shortly thereafter.

If the administration of the corticotropin or steroids were delayed several days after the antigenic challenge, the disease was not suppressed.[20, 59] In the guinea pig, moderate doses of prednisolone, even if given before the antigenic challenge, are reported as failing to suppress the disease.

Since it is impossible to administer these agents in man prior to the appearance of the neurological signs and symptoms, it would seem, as commented on by Koprowski,[47] that this suppressive effect in the experimental animal might well be irrelevant to the human disease.

Two experimental studies, however, suggest that the use of corticotropin or adrenal steroids may be beneficial even if delayed days beyond

the challenge period. Gammon and Dilworth recorded complete recovery in 35 of 51 guinea pigs treated with ACTH after the onset of paralysis.[28] Kibler successfully suppressed the appearance of EAE in rabbits with massive doses of methyl prednisolone, when the drug was delayed eight days following antigenic challenge (three days before onset of the disease in the control animals). The disease appeared when the drug dosage was reduced below 2 mg./kg.[43]

Kibler points out that animals eight days after antigenic challenge (when these animals were treated) have cells which can transmit the disease to unaffected animals, and also have lesions in the central nervous system. The suggestion is made that corticosteroids may indeed have an effect on the basic immune mechanism.

Whether these data bear on human ADE is unknown. If they do, they indicate that discrepancy in reported efficacy of treatment might be related to time of treatment and dosage of drug. It is possible that large doses of drug might be effective when small ones will not. It is also possible that human disease can be effectively treated if caught early, as in the Gammon and Dilworth animals. Possibly relevant to this subject is the experience with ACTH and steroid treatment of the massive myoclonic seizure–hypsarrhythmia syndrome of infancy. Many of these cases are of unknown etiology, and the seizures respond to steroid medication. It has recently been demonstrated that the number of cases with residual mental impairment is directly related to delay in initiation of ACTH or steroid treatment.[35]

The actual role of viral infections and immunity reactions in pathogenic mechanisms of much disease, particularly encephalitis, is unclear at the present in view of data that certain viruses, particularly some of those associated with neurological disease, can be recovered from tissues for long periods of time.[63] Recent data on the persistence of rubella virus and its association with encephalopathy are germane to this point.[58]

Reversal and Prevention of Adrenal Insufficiency or as "Supportive" Agents of Unknown Physiological Mechanism

Extensive study has been afforded the subject of the use of the adrenal cortical steroids as adjunctive therapy in infections. If they could be proved of value as nonspecific agents in these illnesses, they could also be indicated in a wide variety of other illnesses, among which encephalitis might be included. Kass and Finland reviewed the vast literature on the subject in 1957 and concluded only that there was some evidence that under proper circumstances corticosteroids augmented certain aspects of resistance to infection.[42]

It is clear that even patients with bacterial infection in hypotensive collapse rarely suffer from the acute adrenal insufficiency that would be the specific indication for the use of the corticosteroids. Melby and Spink have shown that the plasma 17-hydroxycorticosteroid levels on 22 such patients are in the high normal range.[55] Even in meningococcemia with shock–the Waterhouse-Friderichsen syndrome–the therapeutic value of steroids is debatable, the weight of evidence being that

they are not often helpful.[34, 79] Despite this negative evidence of the "supportive" value of the steroids, however, the physician, as Cope points out, can rarely ascertain, in the case of sudden collapse in a desperately ill patient, whether adrenal insufficiency has occurred, and cortisol must be given empirically.[15] Cope further points out the important paradox that in certain cases hypotensive collapse may be accompanied by the high plasma steroid levels usually encountered in stress, and yet the patient responds clinically to a rapid infusion of hydrocortisone.[15]

Aside from this special situation of acute hypotension, however, present evidence does not appear to justify the use of steroids as supportive agents in acute infections and nonviral encephalitis.

CHOICE OF AGENT

Corticotropin vs. Corticosteroids

THERAPEUTIC EFFECT. Corticotropin has actions other than those of stimulating output of the adrenal corticoids, but there is little doubt that any therapeutic efficacy of these compounds in the disease discussed here derives from the production of increased amounts of adrenal hormone. There have been several reports that the therapeutic response of patients with acute attacks of demyelinating disease to prednisone and cortisone is significantly inferior to that obtained with corticotropin.[3, 65, 82] Cope[15] points out that if corticotropin is compared with oral steroid therapy, the mean plasma hydrocortisone levels are likely to rise higher after corticotropin and to fluctuate less. Field and Miller have demonstrated that in the guinea pig, corticotropin has a superior effect to prednisolone in mitigating experimental allergic encephalomyelitis.[20]

It is of interest that in the clinical treatment of cerebral edema due to neoplasia and trauma, the adrenal steroid analogs have been used ubiquitously in preference to corticotropin.

SIDE EFFECTS. One study showed that the incidence of severe side effects in patients treated with corticotropin is less than in those treated with corticosteroids.[80] This comparative study was performed, however, on patients in whom the daily dose of corticotropin was adjusted to produce a calculated 17-hydroxycorticosteroid excretion, and the doses were therefore not in the high range frequently used for acute disease. Both corticotropin and the adrenal cortical steroids produce a variety of pathophysiological effects, which will be well covered elsewhere in this volume and therefore will be only briefly mentioned here: (1) a mild diabetic tendency, and accentuation of already present diabetes; (2) osteoporosis; (3) delayed wound healing—the latter phenomenon has not proved to be of importance clinically; (4) increased incidence of peptic ulcer, particularly when aspirin is simultaneously administered (many of these patients have in addition an increased tendency to gastrointestinal ulceration because of hypothalamic lesions resulting from their illness and, therefore, a heightened susceptibility

to gastrointestinal bleeding; (5) hypercoagulability of the blood; (6) impaired resistance to infections, due to the anti-inflammatory action; (7) "mooning" of the face; (8) easy bruising; (9) psychological instability, occasionally progressing to manic psychosis; and (10) a possible adverse effect on the developing fetus.

Corticotropin, because of its over-all adrenal stimulating effect, has a tendency to produce more sodium retention and potassium loss than is produced by the adrenal glucocorticoids, particularly the newer analogs.

The Choice of Adrenal Corticosteroid

The over-all evaluation of the newer steroids is dealt with in detail elsewhere in this volume, and therefore will be only briefly discussed here.

The newer synthetic analogs of cortisone achieve a high degree of separation of the mineralocorticoid, or aldosterone, effect from the glucocorticoid, or anti-inflammatory, action. All the newer compounds are highly potent anti-inflammatory agents with minimal sodium retaining and potassium losing properties. But, as Cope points out, "so far no suggestion of a real change in quality of the glucocorticoid actions has been obtained. Included in this group of actions are the anti-inflammatory effects, the anti-allergic, the glycogen-storing action, the protein-losing and the calcium-losing effect on bone. All these actions seem to go together, and they also seem to be inseparable from the inhibitory action of the steroid on the pituitary production of corticotropin."[15]

Both prednisone and prednisolone are synthetic compounds whose glucocorticoid potency is markedly greater than that of hydrocortisone, and whose mineralocorticoid properties are not increased over that compound. 6-Methyl-prednisolone, another newer synthetic analog, has possibly slightly more potency than prednisolone in various clinical disorders, and a mineralocorticoid or sodium retaining action probably slightly less than the parent compound.[83]

The most generally used of the adrenal cortical steroids in the treatment of cerebral edema has been dexamethazone.[5] The therapeutic potency of this drug is approximately seven times that of prednisolone.[10] The occurrence of edema with the use of this drug is rare, and sodium retention is minimal.

Equally potent as an anti-inflammatory agent is triamcinolone, but its use has been accompanied by specific serious side effects—headaches, anorexia, weakness, nausea and muscle wasting of severe degree.[26] Two cases of possible relation of increased intracranial pressure to the use of triamcinolone have been reported.[49]

THE SPECIFIC THERAPEUTIC SITUATIONS

Acute Postinfectious, Postvaccinial, Post-Rabies Vaccine, and Cryptogenic Encephalomyelitis

Review of the clinical data seems to indicate that corticotropin is indicated if the disease process is that of postinfectious, postvaccinial,

post-rabies vaccine or cryptogenic encephalomyelitis. Much in the nature of these entities suggests the similarity to EAE, as has been discussed. Particularly, the presence of myelitis and optic neuritis indicates a close similarity to primary demyelinating disease. Because of some evidence, already reviewed, that early treatment may make a difference in outcome, it is recommended that ACTH, 60 units, be given intravenously daily to patients when the diagnosis is first made, and continued if signs and symptoms diminish, for at least seven days. If no therapeutic effect is seen in three days, the ACTH can be rapidly diminished in dosage and discontinued during the next three days. The same amount of intramuscular ACTH gel can be given once daily, but some authorities feel that the intravenous medication is more effective. The dosage should be stepped down over a period of a week at the termination of treatment. That exogenous ACTH suppresses the normal pituitary-adrenal mechanism must be recognized and the patient should be carefully watched for signs of adrenal insufficiency as the ACTH dosage is reduced. cortisone may be required for a few days at the end of treatment. The longer the treatment has progressed, the greater the danger of prolonged suppression of recovery of normal pituitary adrenal mechanisms.

Acute Cerebral Edema with Increased Intracranial Pressure, Presumably Due to Disseminated Encephalitis, and "Toxic Encephalopathy"

Whether ACTH or adrenal steroids are therapeutic in this situation is unknown, but there is a case, as noted before, to be made for their use. It is reasonable to use in this situation those agents with the most potent anti-inflammatory and the smallest sodium retaining properties: prednisolone or dexamethazone are then to be preferred to ACTH. For adults, prednisolone, in an initial dose of 40 mg. with subsequent doses of 15 mg. four times daily, can be used, or dexamethazone, 10 mg. initially with 4 mg. four times daily to follow. If therapeutic results are not apparent in three or four days, these drugs should be rapidly diminished in dosage. In any case, these large doses must be steadily reduced after 7 to 10 days. If the patient is unconscious and having airway problems, as is so frequently the case, the steroid suppression of the infection-defense mechanism must be feared, and a broad spectrum antibiotic should be administered concomitantly.

The adrenal steroids do not cause rapid reduction in cerebral edema, even in the situations of proved usefulness, such as cerebral tumors. There is a delay of 12 to 18 hours before effect is evident; they therefore do not supplant the hyperosmotic solutions with their almost immediate action.

The steroids should of course be tapered off and stopped as soon as possible. Because the course of medication is usually comparatively short, however, the complication of adrenal unresponsiveness is rarely observed, although adrenal insufficiency must be carefully watched for.

It should be noted that prolonged oral courses of steroids, particularly in small doses, have been associated with marked increases in

intracranial pressure, probably through the mechanism of adrenal insufficiency.[5]

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Newer Drugs in Therapy of Pinworm Infestation

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Ten years ago in the Newer Drugs issue of this journal Bumbalo and Plummer[7] reported on the use of piperazine in the treatment of pinworn and roundworm infections. Piperazine remains as an accepted and useful drug; in fact, Hunter, Frye and Swartzwelder[25] in the 1966 edition of their *Manual of Tropical Medicine* still consider it as the drug of choice. Others either prefer pyrvinium pamoate or rate it as an equal choice with piperazine. In addition to these drugs, two newer agents still in the investigative stage, thiabendazole and stilbazium iodide, will also be evaluated.

The chemotherapy of pinworm infection really began with the use of methylrosanaline (gentian violet) in 1940 and has included a large number of different agents. Bumbalo et al. reported in 1960[8] that they had evaluated ten different drugs, including egressin (thymol-N-isoamylcarbonate), diphenan (parabenzylphenyl carbamate), gentian violet (methylrosanaline HCl), cremothaladine (α-phthalysulfathiazole), carbomycin, garlic, piperazine, promethazine HCl, pyrathiazine and pyrvinium chloride. In addition to these, tetracycline has also enjoyed some use. Many of these drugs are effective in eradicating pinworms but are unsuitable for one reason or another.

The group at the N.I.H. lists the following specifications for a satisfactory treatment against pinworms.[12]

1. The drug must be highly effective in removing pinworms.
2. The drug must be relatively nontoxic.
3. The treatment must not be expensive.
4. The treatment must be easily administered.

To this list should be added:

5. The drug should be reasonably free of side effects.

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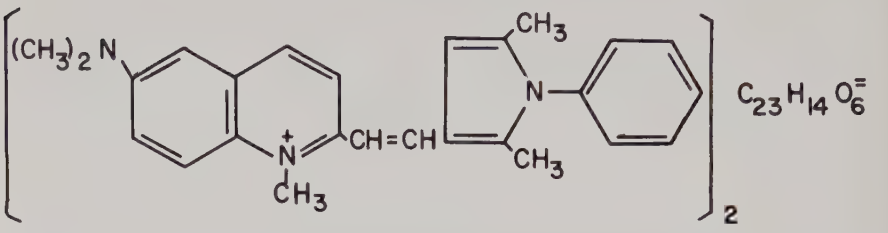
Since excellent reviews of the pinworm problem in general are already available in the literature[4, 12, 27, 28, 39, 48] this paper will be concerned primarily with an evaluation and comparison of the drugs now in use for the treatment of enterobiasis.

PYRVINIUM PAMOATE (POVAN, VANQUIL, POQUIL)



Bis-6-dimethylamino-2[2-(2,5 dimethyl-1 phenyl 3 pyrrol)vinyl] 1 methylquinolinium salt of 4,4′-methylene bis(5 hydroxy-2-napthoic acid).

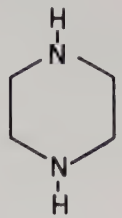
PHARMACOLOGY. This drug is one of a series of cyanide dyes which were first developed as anthelminthics after they were shown to possess antifilarial activity.[5] Their pharmacologic activity is based upon an interference with the respiratory enzyme system of the nematode. The drug was first introduced in the form of pyrvinium chloride and was found to be effective against ascaris, hookworm and whipworm. Its effect against pinworm infestation of mice and rats was reported by Weston in 1953.[50] Royer[38] in 1956 confirmed its effectiveness in humans. The pamoate salt was introduced in 1959. Since it is virtually unabsorbed from the gastrointestinal tract, this salt is much better tolerated and the incidence of nausea and vomiting has been greatly reduced. The chief disadvantage of this drug is the fact that it is a bright red dye which will stain furniture and clothing. It also stains the stool red.

PREPARATIONS AND DOSAGE. Pyrvinium pamoate is marketed in the United States in the form of a suspension or a coated tablet containing 50 mg. of pyrvinium base per tsp. or per tablet. The manufacturer's recommended dosage is a single dose of 5 mg./kg. body weight (1 tsp. or 1 tablet per 22 lb. body weight) up to a maximum of 7 tsp. or tablets.

Many physicians prefer to repeat the dosage in one to three weeks on the basis that the drug kills only the mature worms in the intestinal tract, the second dose acting on the new hatch from ova which were ingested subsequently. Beck in 1964[3] reported a "cure" rate of 98 per cent in a group of 100 patients given a single dose of 2 mg./kg. instead of the previously recommended dose of 5 mg./kg. Beck states, "because of the repeated recurrences of the parasite, periodic wormings are the most efficient method of dealing with the pinworm problem."

TOXICITY AND SIDE EFFECTS. The drug is essentially nontoxic. Side effects are minimal, consisting of abdominal discomfort, nausea and vomiting, and more frequently seen with the suspension than with the tablets. A single case of apparent photosensitization to pyrvinium pamoate has been reported.[35]

PIPERAZINE (ANTEPAR)



PHARMACOLOGY. Because it is an excellent solvent for uric acid, piperazine was first used, though ineffectively, in the treatment of gout. Its anthelminthic properties were first reported in 1949. Piperazine is readily absorbed from the gastrointestinal tract, making it somewhat surprising that it should be effective against a large bowel parasite. The drug narcotizes and paralyzes but does not kill the worm, allowing retained worms to recover. This is the basis of the seven-day therapy with this drug to insure elimination of all of the parasites.

PREPARATIONS AND DOSAGE. Piperazine is available as piperazine citrate in the form of a tablet equivalent to 500 mg. piperazine hexahydrate per tablet. The syrup contains a similar dose per teaspoonful, and a flavored chewable wafer of piperazine phosphate also contains the equivalent of 500 mg. piperazine hexahydrate. The recommended dosage is 250 mg. per 15 lb. body weight up to a maximum of 2 gm. given once daily in the morning for seven consecutive days. No laxatives, enemas or special diets are recommended by the manufacturer. A regimen of two single doses of 5 gm. each, given one week apart was found by Mathies[28] to be less effective and more toxic than the conventional schedule.

TOXICITY AND SIDE EFFECTS. There is a wide range between the therapeutic and toxic dose of this drug. Bumbalo[7] reported only one case of urticaria and three cases of nausea and vomiting among close to 500 children treated. Transient neurological side effects have been reported in two patients who were suffering from chronic renal disease. The drug has been used in pregnancy without ill effect.

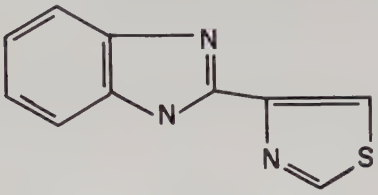
PRIPSEN GRANULES

Not a new drug but simply a combination of piperazine phosphate and a cathartic (Senkote), Pripsen is said to be effective as a single dose because of its ability to empty the intestinal tract of the worms while they are still narcotized. The drug has never been marketed in the United States but is available for investigational use. It is apparently being used in England.[1] The drug is supplied in the form of chocolate-flavored granules containing 1 gm. piperazine phosphate and the equivalent of 7.5 mg. of sennosides A and B. Dosage has varied among different investigators. Bumbalo[10] gave 2 tsp. to children aged two or younger, 3 tsp. between ages two and five and 4 tsp. (4 gm. piperazine) to all patients over five years of age. He states, "the minimal consistently

effective dose of any piperazine preparation in the treatment of pinworm infection should be 3 gm."

Cure rates of 80 to 90 per cent have been reported, but with some side effects of abdominal cramps and frequent bowel movements. A newer preparation containing 1 gm. piperazine and 375 mg. senna (3.75 mg. sennosides) per tsp. has been reported to have markedly reduced the incidence of abdominal cramps and loose bowel movements.[20]

THIABENDAZOLE (MINTEZOL)



$(C_{10}H_7N_3S)$

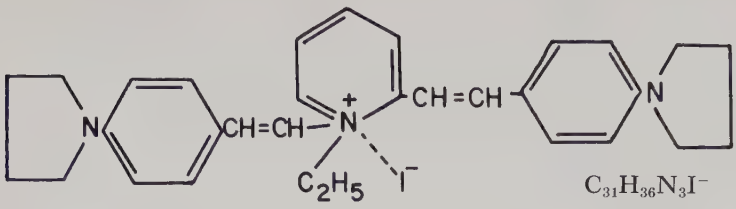
This drug—2-(4′ thiazolyl)-benzimidazole—was developed as a result of investigation of the anthelminthic activity of several hundred benzimidazole compounds. These compounds are among the most potent chemotherapeutic agents known. Thiabendazole is a white tasteless crystalline compound which is stable both as a solid and in solution. It is slightly soluble in water. The drug shows activity in vitro at a concentration of 10.5 μg. per ml. Developed first as a veterinary drug, thiabendazole was reported to have anthelminthic properties against human infestations with ascaris, trichuris and oxyuris. The absence of activity against other microorganisms and negligible mammalian toxicity suggest that the mode of action of this drug is through a unique interference with a metabolic pathway essential to a variety of helminths.

PREPARATION AND DOSAGE. The use of this drug has been limited to clinical investigation. The only studies to date on the use of thiabendazole in pinworm infestations in this country have been reported by Davis.[13] The drug was administered in the form of a chewable wafer or a marshmallow-flavored suspension containing 500 mg. thiabendazole per wafer or tsp. The dosage used was 50 mg./kg. per day (up to a maximum of 2.0 gm.) for two days. The daily dose was usually divided into two doses of 25 mg./kg. to reduce the incidence of side effects, particularly nausea.

TOXICITY AND SIDE EFFECTS. The drug is rapidly absorbed after oral administration. Approximately 95 per cent of the absorbed drug is metabolized and excreted by the kidney as the hydroxylated (5 position) derivative. To date there has been no reported evidence of hematopoietic, liver or renal damage.

Side effects are usually mild but occur in 15 to 30 per cent of patients treated. They include anorexia, nausea, occasionally vomiting, and dizziness. The suspension seemed better tolerated than the wafers.

STILBAZIUM IODIDE (MONOPAR)



$C_{31}H_{36}N_3I^-$

2,6,Bis(p-pyrolidinostyril) pyridine ethiodide.

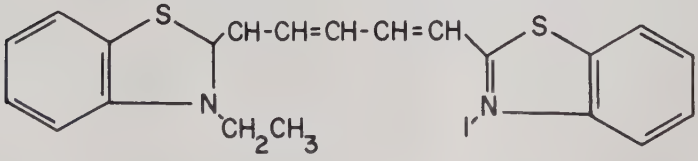
PHARMACOLOGY. Stilbazium iodide is a tasteless, nearly insoluble quaternary pyridine. It is relatively nontoxic. Large doses in animals produce only a depression in appetite and a failure to gain weight. No toxic effects could be demonstrated on liver, kidney or other organs at autopsy. The mode of action of this drug on pinworm has not been determined, but from some in vitro experiments it appears to cause death when it reaches the circumesophageal nerve ring of the parasite.[11]

PREPARATION AND DOSAGE. This drug was investigated temporarily in the United States. Reports appearing in 1963 indicated that when given in a single dose of from 5 to 21 mg./kg. it was practically 100 per cent effective.

TOXICITY AND SIDE EFFECTS. When the drug is given in gelatin-filled capsules, mild nausea and vomiting occurred in 13 to 25 per cent of cases, but when given as an enteric coated preparation there were no side effects noted.[26, 49] A recent personal communication from the manufacturer[19] reports, "We have temporarily discontinued clinical trials with this drug for purely pharmaceutical reasons. London, however, is continuing its investigation. . . ."

From the reports now available in the literature this drug would seem to warrant further clinical trial.

DITHIAZANINE IODINE (DELVEX)



3,3'Diethyl thiadicarbocyanine iodide, a cyanine dye with an intense blue color, was developed from a study of the anthelminthic activity of cyanine dyes against filaria. Its mode of action is to interfere with respiratory enzyme systems in the parasite. Although highly effective against oxyuriasis as well as certain other parasitic infestations, it produces side effects of anorexia, nausea, vomiting and abdominal cramps in about one third of patients. More important, eight deaths have been reported with the use of this drug, some following a dose as

Table 1. *Comparison of Drugs Used in Pinworm Infestation*

DRUG	AUTHOR	DOSAGE	CASES	% CURES	% SIDE EFFECTS
Pyrvinium pamoate	Royer[39]	5 mg./kg.	138	100	1.5
	Bumbalo[8]	5 mg./kg.	17	100	
	Davis[13]	5 mg./kg.	103	98	4.0
	Turner[46]		65	95	5.4
	Beck[2]	5 mg./kg.	100	96	
	Beck[3]	2 mg./kg.	100	98	
Piperazine citrate	Bumbalo & others (as summarized by Bumbalo[7])	25 mg./kg.	597	93	< 1.0
Piperazine and senna	Edge[15]	2 to 4 gm. piperazine according to age	102	84	2
	Bumbalo[10]	2 to 4 gm. piperazine	60	88	
Thiabendazole	Davis[13]	50 mg./kg./day for 2 days	100	97	15–30
Stilbazium iodide	Wagner[49]	10 to 15 mg./kg.	72	95	25, capsules 0, enteric coated
	Jeffrey[26]	10 mg./kg.	30	100	13, capsules 0, enteric coated
	Hsieh[24]	10 mg./kg.	33	94	

low as 100 mg.[37] Therefore *dithiazanine should not be used in the treatment of oxyuriasis.*[16]

CONCLUSIONS

There are two effective drugs now available for the treatment of pinworm infestation. Pyrvinium pamoate, effective in a single dose, is probably the drug of choice. Piperazine, also an excellent remedy, must be given daily for seven days. Two new investigational drugs, thiabendazole and stilbazium iodide, both seem to be effective but have not been released for use in this country. A partial comparison of the effect of these drugs as reported by various authors is outlined in Table 1.

The nature of the life cycle of the pinworm, the difficulty of eliminating the eggs from the environment, and the constant reinfection make eradication of this parasite at times impossible despite adequate medication. In certain instances it is probably wise to treat whole families at once, but in cases of repeated recurrence the simplest possible therapeutic regimen should be employed, and then only if the infestation is symptomatic. Most,[31] in discussing the asymptomatic carrier and the problem of institutional infestation says: "The importance of its (pinworm) eradication should be de-emphasized, and it is the responsibility of the pediatrician and the general practitioner to know and do this."

SUMMARY

1. Pyrivinium pamoate (Povan) is the present drug of choice in the therapy of pinworm infestation.

2. Piperazine is still an accepted and effective drug.

3. Thiabendazole and stilbazium iodide have both shown therapeutic efficiency but have not been released for commercial use.

4. General hygienic measures and social conditions are often more important than any drug therapy and may render any medication ineffectual.

5. In some situations pinworm infestation should be accepted as inevitable and no effort made to treat the asymptomatic patients.

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An Updated Look at Antirheumatic Drugs

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Clinical control of the various rheumatic diseases is dependent to a great extent on empirical therapy with drugs whose action may not be at all clear. To say that a drug has anti-inflammatory or antirheumatic activity is almost a play on words, because the mechanism of that action is largely unknown and the observed clinical effect of the drug on inflammation or rheumatic activity is the sole basis for such a designation. For example, colchicine, which has been in use for centuries, is believed to have a specific anti-inflammatory effect in gout, but the actual mechanisms of producing this effect are understood very poorly, if at all. Therefore in judging the relative values of various antirheumatic drugs, one must recognize that such assessment is based largely on clinical evaluation, which by its very nature cannot have sharp delineations or yield precise results – all of which makes drug evaluation difficult and a sometimes frustrating experience.

Salicylates

Although aspirin has long been regarded as indispensable in the treatment of rheumatic disease, there has been an increasing awareness of its irritating and ulcerogenic action on the gastric mucosa. These side effects, together with the unpleasant and often unacceptable (though reversible) tinnitus and deafness, have limited more effective clinical application of salicylates because of the necessity for dosage restrictions. The maintenance of blood salicylate at a level of 20 to 30 mg./100 ml. is generally advocated, but in many patients this is not possible over prolonged periods because of the development of one or another unpleasant side effect. In order to maintain such a blood level, it is usually necessary to prescribe about 4 gm. daily, but on long-term therapy, most patients are unable to accept more than 2.5 to 3 gm. as a total daily dose of aspirin. With present methods, I do not believe that blood salicylate levels are worthwhile or needed in routine practice.

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In the patient with rheumatoid arthritis, it is usually imperative to get the salicylate radical into the body in some way or other. The use of enteric-coated sodium salicylate is generally unsatisfactory because of poor or capricious absorption and the lesser benefits from the sodium salt. Often, the gastric irritation of aspirin can be avoided by the use of the buffered form, each tablet usually containing the same amount of acetylsalicylic acid as the regular aspirin tablet. Occasionally gastric irritation can be avoided by the use of a liquid in the form of choline salicylate, which is made up to yield 0.3 gm. of salicylate per teaspoon.

Enteric coating of aspirin has thus far been an insurmountable pharmaceutical problem, but this has been circumvented quite satisfactorily by the use of a special cellulose coating (marketed as Ecotrin). This tablet contains 0.3 gm. acetylsalicylic acid. The cover yields only to pancreatic proteolytic enzyme in the usual patient and provides slow leakage of the drug out of the tablet as it moves down the gut. However in a small percentage of patients, the tablet apparently remains in the stomach long enough for appreciable amounts of aspirin to be released and give rise to the same gastric irritation as the plain aspirin tablet; it is important for the clinician to be aware of this limitation.

One possible side effect of high-dosage salicylate therapy may be a stimulation of the respiratory center and production of low-grade hyperventilation. Patients with rheumatoid arthritis commonly have a hyperfunction of the sympathetic nervous system. If vigorous salicylate therapy in high dosage would stimulate even a mild degree of hyperventilation symptoms, it seems reasonable to expect that this would compound the problem of fear and anxiety. The discerning clinician will at least be on guard for this possibility. In this regard, it should be added that the prescribing of mild sedation for the rheumatoid arthritic (such as phenobarbital, 15 mg. four times a day) is an essential part of the basic therapy program.

Corticosteroids

It is an indisputable fact that in the category of drugs thought to have anti-inflammatory and antirheumatic effect, corticosteroids are the most potent and decisive, and the most consistently predictable, and they may indeed be used as a base for titration of the relative effectiveness of all other such drugs. Corticosteroids have been in general clinical use since 1950 and are well known to all practicing physicians. Unfortunately, the analogues of hydrocortisone have been found to produce many of the serious complications and adverse effects which resulted from the abuse of the parent compound, and this in turn gave rise to the misconception that they are all basically the same in action, offering no therapeutic advantages. This is not true; on the contrary, there are qualitative differences which the clinician should exploit so that the patient may derive the maximum advantages and be liable to the minimum hazards of "steroid therapy."

Hydrocortisone therapy created serious problems in a high percentage of patients because of sodium and water retention and potassium loss. The development of prednisone reduced this problem

considerably, but in an appreciable number of patients, prednisone too caused distressing retention of sodium and water. Prednisone is still the steroid of choice in most patients because it is the least expensive and, generally speaking, produces the fewest complications. However, when prednisone does cause extracellular fluid accumulation or the very occasional idiosyncratic side effect, triamcinolone or dexamethasone may be substituted to advantage. Triamcinolone does not cause retention of sodium and water and in some cases may actually promote water excretion. Its anti-inflammatory dose ratio is 4 mg. for each 5 mg. of prednisone. Triamcinolone has potent appetite-suppressant action and should be avoided in the underweight patient. In an occasional patient, triamcinolone may cause a general weakness and malaise as well as varying degrees of myasthenia and of potassium deficiency.

On the other hand, dexamethasone may be superior to prednisone in the thin asthenic arthritic because of its very potent, appetite-stimulating action (Fig. 1). It also has a tendency to elevate the mood, in contrast to the sometimes mood-depressing effect of triamcinolone. In dosage, 0.75 mg. of dexamethasone is equivalent to 5 mg. of prednisone. Infrequently, dexamethasone may cause considerable extracellular fluid accumulation.

Before leaving the subject of corticosteroid therapy, it should be emphasized that occasionally the clinician may find that a certain

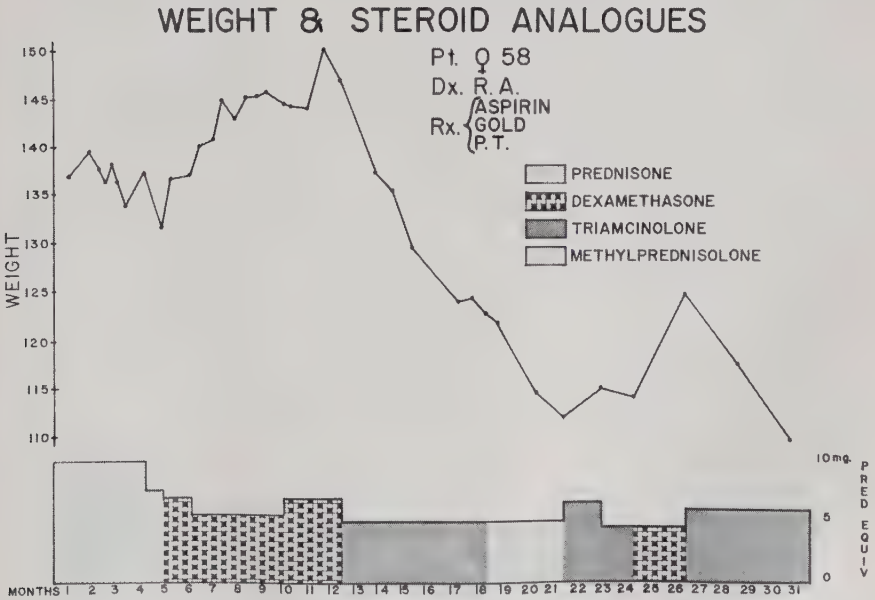

Figure 1. Graph of "dry" weight (no edema) of a 58 year old woman with classical rheumatoid arthritis. During the period of 31 months of observation, note the slight decline while on prednisone, the prompt and striking weight gain on dexamethasone, and the precipitous fall on triamcinolone. There was a prompt gain of 12 pounds during the period of only 2 months' therapy with dexamethasone. All steroid dosages are given in prednisone equivalents, as indicated by the scale on the right.

analogue is apparently ineffective. This should not be a reason for "giving up" on corticosteroid therapy; on the contrary, another analogue may be substituted with surprising success. If other corticosteroid analogues are apparently ineffective, a final trial should be given with corticotropin gel; maintenance of steroid benefit can sometimes be achieved by giving the patient 20 units intramuscularly every 48 or 72 hours.

Unreasoning fear with total avoidance of corticosteroids in rheumatoid arthritis is no more justified than is abuse by their overdosage. Just because there have been instances, however numerous in the past, of serious side effects from flagrant abuse of corticosteroids, one should not go to the opposite extreme and deprive a patient with crippling rheumatoid disease of the much needed small doses of these agents. Often, very small doses (e.g., prednisone, 2.5 mg. once daily in the morning or 1 mg. three times a day) may be the difference between productivity and severe disability. The physician must keep in mind that corticosteroid should not be the first or initiating treatment of the arthritic, nor should it ever be given alone, but only as a part of the overall therapeutic program. Corticosteroids should be prescribed individually and not as a part of a combination tablet, such as with aspirin or phenylbutazone. Usually small divided doses are most effective, but occasionally, this should be varied according to the patient's needs. One patient may need only a single small dose in the early morning, immediately upon awakening, to mitigate and shorten the extremely severe early morning stiffness; another patient may experience his most trying symptoms in the evening, when the steroids should be given immediately after dinner, or during the night, when the steroids should be given at bedtime. Most patients with rheumatoid arthritis will do best with small divided doses, as indicated in the foregoing.

Injections of long-acting corticosteroids are unwise and have no place in managing rheumatoid arthritis. The same can be said about alternating daily dosage – that is, one day a large dose and the next day none. It is my belief that there is no sound basis for this type of steroid prescription and it only works a great hardship on the patient. Lastly, it cannot be emphasized too often or too strongly that long-term corticosteroid therapy of rheumatoid arthritis carries with it an implied dosage ceiling of the equivalent of 7.5 to 10 mg. of prednisone as a total daily dose, and under no circumstances should this maximum be exceeded in any maintenance therapy considerations. Since corticosteroids are basically catabolic, a strong anticatabolic program of therapy should be maintained in any patient taking them. This is principally in the form of gonadal hormone therapy, with special emphasis on testosterone and its analogues, although estrogens should be included. The use of a high-protein diet with adequate calcium intake, the supplementation with vitamins and even the parenteral injection of vitamin B_{12} are all anticatabolic measures worthy of use. Physical therapy, especially exercises and muscle massage, must also be considered in the category of anticatabolic therapy.

Allopurinol

Prophylactic therapy is of course preferred in the treatment of metabolic diseases, but if that is not possible, the goal next in importance is the blocking of the abnormal physiologic mechanism responsible for the disease. This has been achieved in gout with the use of allopurinol. The basic abnormality of this disease is the excessive accumulation of uric acid in the body; uric acid is formed from xanthine and hypoxanthine by the catalytic action of the enzyme xanthine oxidase. The action of this enzyme is effectively blocked (inhibited or diverted?) by the ingestion of the drug allopurinol, which is the isomer of hypoxanthine. Apparently the conversion of allopurinol to allo-xanthine is carried out by the preferential action of xanthine oxidase (Fig. 2). If enough allopurinol is administered, the body's available supply of xanthine oxidase will be largely utilized in the conversion of allopurinol to allo-xanthine, leaving little for the conversion of xanthine and hypoxanthine to uric acid.

Thus allopurinol offers a more basic control of hyperuricemia and gout than do the uricosuric drugs. The renal excretion of allopurinol and its breakdown product, allo-xanthine, and the increased load of xanthine and hypoxanthine, are without problems or complications. In fact, surprisingly few adverse reactions of any kind have been reported from allopurinol administration. Some patients have developed skin rash,

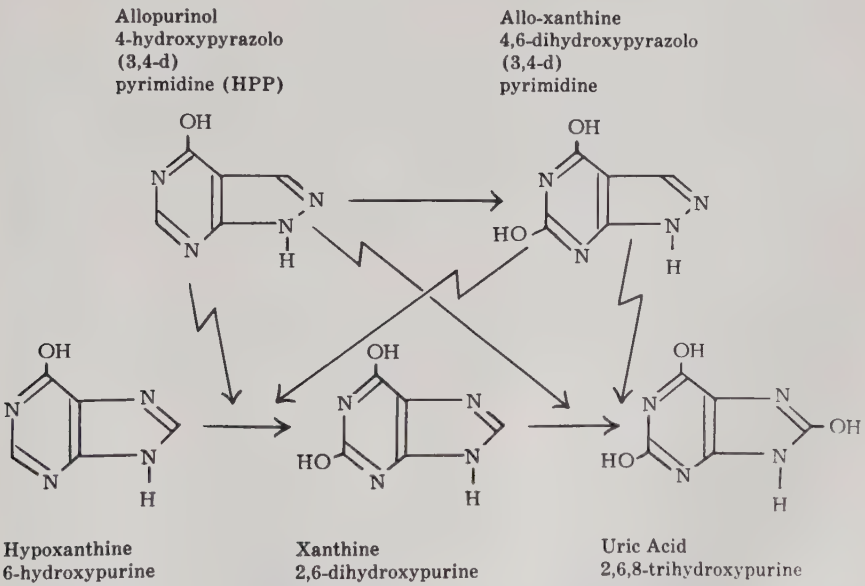

Figure 2. The chemical similarity of allopurinol to hypoxanthine is evident. The figure is intended to show a preferential chemical reaction of allopurinol conversion to allo-xanthine, while at the same time, both of these inhibit the conversion of hypoxanthine through xanthine to uric acid. (From Rundles, R. W., Elion, G. B., and Hitchings, G. H.: Allopurinol in the treatment of gout and secondary hyperuricemia. Bull. Rheum. Dis. *16*: 402, 1966, with permission of the publishers.)

usually maculopapular but occasionally more severe forms. There have been occasional cases of gastrointestinal upset, but not of any serious proportions. As with many drugs, there is the rare idiosyncratic effect associated with systemic manifestations of chills, fever, nausea, vomiting, skin rash, alterations of leukocyte count, arthralgia and so forth. The expected accumulation of xanthine and hypoxanthine in the body has not created any pathologic problems, and the excretion of these products in the urine usually is reported to be less, proportionately, than the fall in urinary uric acid. This is believed to be related to inhibition of purine biosynthesis and to reutilization of hypoxanthine and xanthine; both of these actions may be considered to have a neutralizing effect of the basic defect of overproduction of uric acid and may thereby be regarded as an additional advantage of allopurinol therapy.

Allopurinol is available as a 100 mg. tablet and initially may be prescribed as one tablet three times daily. In the more severe cases where hyperuricemia is not controlled, the dose may be increased to two or even three tablets three times daily. For unknown reasons, attacks of acute gout often occur with increased frequency during the early stages of allopurinol therapy and, therefore, it is wise to start the individual simultaneously on colchicine in a dose of 1 tablet (0.5 mg.) two or three times daily. Continued administration of uricosuric drugs is strongly recommended for the first six months of therapy; afterwards they should no longer be necessary.

Indomethacin

With evidence accumulating to suggest some type of derangement of tryptophan metabolism in rheumatoid arthritis, interest began to focus on indole derivatives as possible sources of therapy. Several such compounds have been developed but only indomethacin has shown promise of clinical value. Mefanamic and flufenamic acid, which are derivatives of anthranilic acid, have been found to have anti-inflammatory properties in laboratory animals but have had limited usefulness in human disease.

Animal studies demonstrated potent anti-inflammatory activity of indomethacin when compared to corticosteroids, aspirin and phenylbutazone as measured by the cotton pellet, carrageenin, and other synthetic forms of induced inflammation, but no toxic effects were observed except for intestinal ulcerations and hemorrhage with massive oral doses.

It has been demonstrated that the drug is rapidly absorbed and peak blood levels are obtained within an hour. The drug is excreted rapidly and principally in the urine, mostly in the conjugated form, and has virtually disappeared from the blood within 5 hours. Only trace amounts were found in the bile. Except for the stomach, there was no evidence of any harmful effects on the visceral organs or on the bone marrow.

Clinical trials have shown that adverse effects of indomethacin are limited to the cerebral and gastric areas. The cerebral side effects consist of headaches (sometimes quite violent), lightheadedness, un-

steadiness, muzziness and sometimes feelings of detachment; these are transient, disappear promptly on discontinuing the drug and leave no harmful residual effects. These side effects are curiously most common in the morning and can be avoided by giving the first dose with lunch and the largest dose at bedtime with milk. The gastric side effects consist of mild to severe epigastric pain and sometimes burning; gastric ulcers have been reported with higher frequency than would be expected in the untreated rheumatoid arthritic. The gastric side effects can be avoided to a great extent by giving the medication on a full stomach and with liberal amounts of milk at bedtime. Therapy should start with 25 mg. two or three times daily, best given at lunch, dinner and bedtime, or 25 mg. can be given with lunch and then 50 mg. with a glass of milk at bedtime. Increases in dosage should not usually be oftener than once a week and in increments of 25 mg. There are great variations in tolerance to this drug: some patients can take 200 mg. or more daily for years without ill effects, while other patients develop distressing cerebral or gastric side effects on 75 mg. or even 50 mg. daily. Isolated cases of dermatitis, somnolence, insomnia, irritable colon and a few other idiosyncratic effects have been observed or reported.

Indomethacin has been found to be highly effective and may be considered the treatment of choice in ankylosing (rheumatoid) spondy-

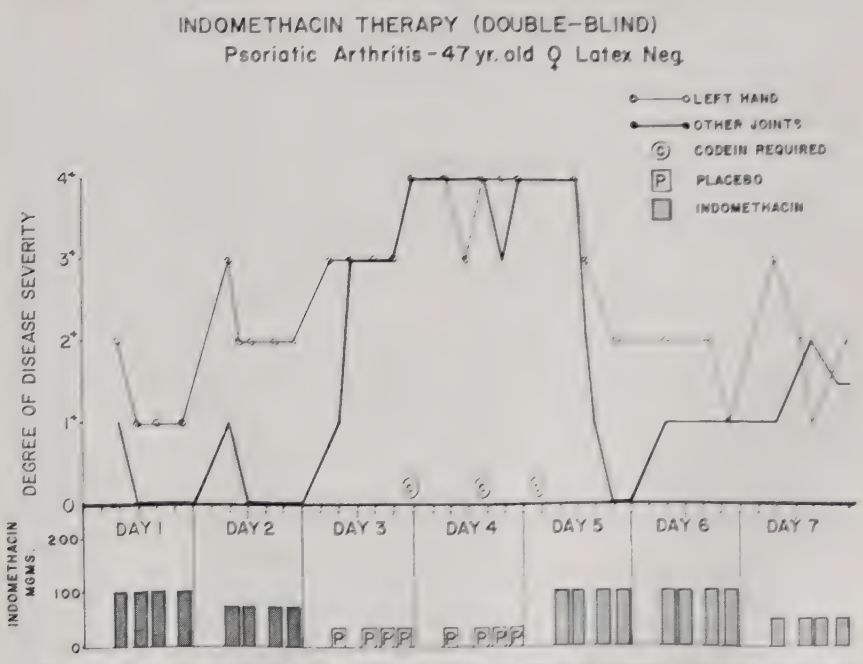

Figure 3. A double blind study with graphing of disease activity (the left hand was most severely involved and therefore was graphed separately). Note the prompt and severe exacerbation of the disease on placebo, requiring the use of codeine for control of pain. There was prompt recovery after the active drug was reinstituted (From Rothermich, N. O.: An extended study of indomethacin. II. Clinical therapy. J.A.M.A. 195:1103, 1966, with permission of the publishers.)

litis; effective control of the disease may be obtained with as little as 50 mg. daily. Much the same can be said for psoriatic arthritis (Fig. 3) and for the chronic polyarthritis associated with gout, although daily maintenance doses of 150 to 200 mg. may be required. Acute attacks of gout are effectively treated with indomethacin but in larger dosage: 50 mg. every two hours for three or four doses. The drug is reported to be highly effective in osteoarthritis of the hip; the reasons for this are not entirely clear, but the percentage of good results is impressive.

Use of indomethacin in rheumatoid arthritis is somewhat more controversial. In my own experience, the results have been most gratifying. For example, a large number of patients who had been on maintenance corticosteroid therapy for long periods of time, were able to have the corticosteroid discontinued entirely or the dose reduced by 50 per cent. Patients with rheumatoid arthritis who do not respond to the basic program of therapy, including rest, salicylates and physical therapy, should be given a trial with indomethacin beginning with a dose of 25 mg. twice daily. The dose may be increased gradually to as high as 150 or 250 mg. daily, due care and precautions being given to the dangers of cerebral and gastric side effects. If the arthritis is appreciably benefited, the drug should be continued on an indefinite basis. Indomethacin may be taken for long periods of time, as much as five years, without apparent ill effects.

Immunosuppressive Drugs

There is controversy as to whether rheumatoid arthritis is an autoimmune disease. The belief that it may be has led to a search for a safe immunosuppressive agent which could have real therapeutic effect. The premise for this therapy is a fascinating and attractive one but not entirely sound or scientific. If a patient with rheumatoid arthritis has for unknown reasons developed antibodies to some of his normal tissue constituents, or if, for equally unknown reasons, his physiologic apparatus produces substances which are antigenic and hence pathologic, it is believed that this "immune" reaction, (or perhaps the abnormal protein which results from it), may be productive of the pathologic alterations characteristic of rheumatoid arthritis. The premise is that if this "immune" reaction can be blocked, the disease process should be interrupted. However, unless the immunosuppressive agent has a fortuitous, selective blocking action on only one such immune process, it would be logical to expect that such an agent would have the same blocking action on all of the body's immune mechanisms. The result would be immunologic chaos for the individual concerned. Indeed, such is sometimes the case when corticosteroids are given in high doses. Nevertheless, the concept of immunosuppression and blocking of inflammatory reaction is the basis for the clinical trial of several such agents.

NITROGEN MUSTARD. Probably the first of this group to be tried was nitrogen mustard, given intravenously for its systemic effect and intra-articularly for its local effect. Good results were reported but could not be confirmed elsewhere with any great consistency, and nitrogen mus-

tard given by either route has not yet met with widespread favorable acceptance.

AZATHIOPRINE. Azathioprine has been employed in hematology and to block kidney homograft rejection for several years. If the daily dose is kept below 150 mg., no harmful effects appear. We have treated 25 patients with rheumatoid arthritis for 6 months or longer using placebo controls. Extensive serologic testing for immune reactions showed no effect on anti-DNA and anti-RNA titers; the quality of gamma globulin was not altered. Responsiveness to typhoid antigen was not altered. Despite the failure to affect measurable immunologic processes, there was startling indication of clinical benefit. This did not, however, seem to be of sufficient degree to warrant general usage in rheumatology. Further studies with azathioprine are warranted and planned.

CYCLOPHOSPHAMIDE. Quite recently, it has been reported that cyclophosphamide may be an effective therapeutic agent in rheumatoid arthritis. This drug has been used for many years in hematology, principally in the lymphomas. In hematologic diseases, it is administered usually in a dose of 50 to 150 mg. daily without undue ill effects. In the above-mentioned report, this same dosage schedule was employed in 38 patients with rheumatoid arthritis, and in most of the cases striking benefit was obtained (with disease remission in nine patients!). This report is so recent that there has not been time for confirmatory studies, and the use of this drug in rheumatoid arthritis must still be considered experimental.

METHOTREXATE. Also within very recent date, there have been reports of a limited number of cases of inflammatory polyarthritis benefited by treatment with methotrexate, which is another immune-blocking agent. Similarly, this drug had been in use previously, being employed by dermatologists in the treatment of psoriasis. It is thought to be a highly toxic drug and great care must be taken to guard against hepatic and bone marrow toxicity.

Chloroquine

The chloroquine group of antimalarials has been used with appreciable therapeutic benefit in disseminated lupus erythematosus and other sun-sensitive conditions, and this led to its trial in rheumatoid arthritis. However, in the latter condition, the benefits are not so clear-cut, despite long trials. On the other hand, the numerous reports of chloroquine-induced retinopathy, leading to impairment of vision, have prompted the appearance of editorials in several journals, urging caution, frequent ophthalmologic consultation and low dosage. Unfortunately, frequent eye examinations give only a false sense of security. *It has been repeatedly demonstrated that by the time the retinopathy is detected, there is so much accumulation of chloroquine in the body, especially stored in the liver, that progression and worsening of the retinopathy may continue for months or years after medication has been discontinued.* Of course the lay person regards blindness as a catastrophe second only to death itself, and forewarning the patient of

the potential effect on vision is the physician's obligation. These considerations certainly pose the question "Do the chloroquines have any place in the therapeutic regimen for rheumatoid arthritis?" In my opinion, they do not.

Summary

Antirheumatic drugs may be of great help in the management of various rheumatic diseases, if they are used with a keen awareness of their hazards and with proper respect for dosage and prophylactic precaution against side effects. It is my belief that the exudative inflammatory reaction in rheumatoid arthritis can be altered, so that the disease can be slowed down or even brought to quiescence or remission, and deformities and disabilities can be delayed, postponed or even avoided. If it were true, as stated by some, that the disease cannot be altered by drugs, one would be hard pressed to justify the administration of any drug other than pure analgesics. Pity the rheumatoid if such an attitude were to prevail!

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Newer Drugs in the Treatment of Cardiac Arrhythmia

ROBERT D. CONN, M.D.*

During the past three years several changes have occurred in clinical cardiology which have completely altered the approach to cardiac arrhythmias. The introduction of synchronized direct-current countershock has in many ways replaced or altered the drug therapy in the management of acute arrhythmias, and the use of transvenous or permanent cardiac pacemakers has greatly limited the use of drugs in the management of heart block. Aside from the application of electronics in medicine, many new aspects of clinical practice have created demands for newer drugs in the therapy of cardiac arrhythmias. Potent new diuretics resulting in marked potassium loss probably are responsible for the apparent increase in cardiac arrhythmias from digitalis toxicity. The increasing frequency of cardiac surgery, and the ever present arrhythmia associated with direct cardiac manipulation, plus the lability of the postoperative physiologic state, have made the search for short-acting and less toxic drugs mandatory. Finally the advent of the coronary care unit, designed primarily to detect and prevent life-threatening arrhythmias, has resulted in a re-evaluation of available drug therapy, and a search for new agents to replace or supplement time-honored but potentially toxic antiarrhythmic drugs. In this setting three drugs—the beta sympathetic blocking agent propranolol (Inderal), diphenylhydantoin (Dilantin), and lidocaine (Xylocaine)—have been used extensively and have gained widespread acceptance as potent and effective adjuncts in the therapy of cardiac arrhythmias.

BETA SYMPATHETIC BLOCKING AGENTS

The medical literature is now replete with information regarding the two different forms of receptor activity in the sympathetic nervous system. The alpha adrenergic receptors[2] are responsible for constriction

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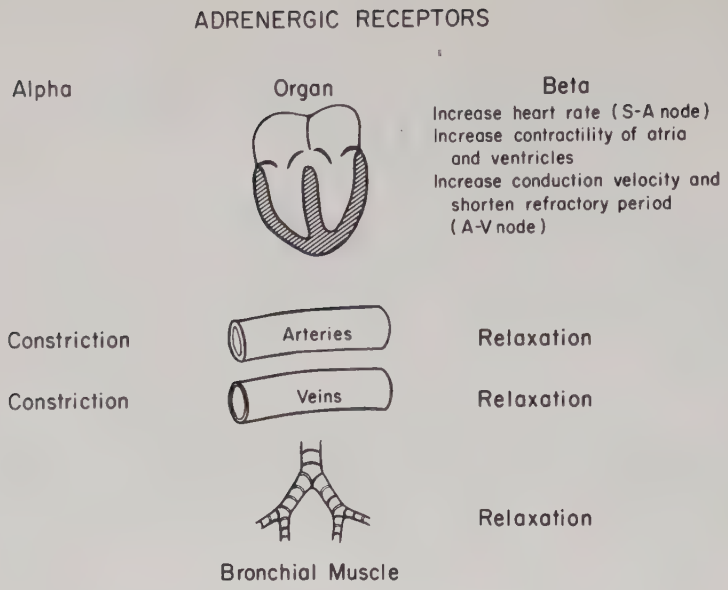
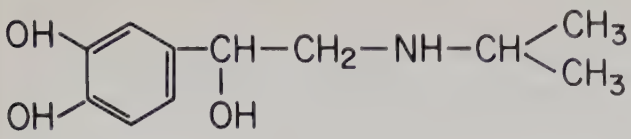


Figure 1.

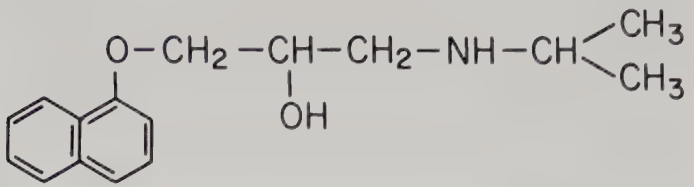
of the smooth muscle of blood vessels supplying skeletal muscle, the splanchnic bed, skin and mucosa (Fig. 1). When stimulated these receptors also result in contraction of the sphincters of the stomach, intestine, urinary bladder, and radial muscle of the iris. The alpha adrenergic receptors are blocked by such drugs as the ergot derivatives, phenoxybenzamine (Dibenzyline) and dibenamine. In contrast the beta receptors[2] (Fig. 1) generally mediate relaxation of the smooth muscle of the arteries, veins and bronchi. These receptors have an excitatory effect upon the S-A node, resulting in an increased heart rate, increased conduction through the A-V node, and increased contractility of both atria and ventricles. In addition they mediate epinephrine-like effects on glucose and fatty acid metabolism.[40] The beta receptors are responsible for relaxation of the ciliary muscle of the eye and the detrusor muscle of the urinary bladder. They have not been found to have an effect upon the gastrointestinal sphincters.[3] Only in recent years have specific beta receptor blocking agents become available for clinical investigation.

General Pharmacology

The beta sympathetic blocking agents are chemically related to the most potent beta stimulating agent, isoproterenol (Fig. 2). The mechanism of receptor blockade is by competitive inhibition, and is highly specific, so that the cardiac effects of calcium, digitalis or the xanthines are not abolished.[12] Likewise the vasodilating effects of histamine, nitroglycerin and acetylcholine are not blocked by these agents.[6, 45] The sterical configuration of the molecule is responsible for its actions and its specificity. The levo isomers have greater beta adrenergic block-



Isoproterenol



Propranolol

Figure 2.

ing activity than the racemic or the dextro forms.[30, 74] The chemistry of the ring structure determines whether the compound is a beta adrenergic stimulating compound or a beta adrenergic blocker.[4, 37] Several beta adrenergic blocking agents have been utilized in the past but have been abandoned because of associated beta stimulating effects or because of undesirable oncogenic properties in laboratory animals.[48] Currently propranolol (Inderal) is the only agent that is used clinically.

Cardiovascular Pharmacology

Two different mechanisms appear to be responsible for the antiarrhythmic effects of these agents. Many of the antiarrhythmic responses can be directly attributed to beta adrenergic blockade.[12, 57] On the other hand these agents have direct effects on the myocardium exclusive of beta receptor blockade. Propranolol has been shown to have properties in common with other antiarrhythmic agents by interfering in some way with the sudden increase in sodium conductance on excitation.[72] At the cellular level it resembles other antiarrhythmic drugs and local anesthetic agents by decreasing the rate and rise of the action potential without altering the resting action potential or changing the phase of repolarization.[72] The beta blocking agents show antiarrhythmic properties in isolated heart muscle similar to quinidine and are capable of reverting digitalis-induced arrhythmias in catecholamine-depleted animals.[56, 71] In addition the dextro isomers, which have very little beta blocking activity, are as effective against digitalis induced arrhythmias as the more potent racemic forms.[30, 39] The direct antiarrhythmic properties of these agents are not unexpected, because they contain a ring group connected to a tertiary nitrogen similar to quinidine and procainamide.

Beta adrenergic blockade results in striking alterations in cardiac function. The resting and exercise heart rate is predictably reduced, by

an average of 20 per cent,[15, 21, 25, 75] and cardiac output is reduced, often in proportion to the reduction in heart rate.[21, 57, 59, 75] Left ventricular work, tension, mean systolic force and end diastolic pressure may all be diminished.[75] The net effect is to significantly reduce the oxygen consumption of the heart.[21, 75] In normal subjects beta blockade reduces exercise capacity by as much as 40 per cent, and may reduce maximal oxygen consumption.[21] In patients, however, beta blockade may actually improve exercise capacity by reducing arrhythmia.[15] In the supine position, systolic and diastolic volumes have been reduced by beta blockade, presumably due to venous constriction and peripheral pooling.[75] In the upright position, however, cardiac dimensions increase with beta blockade.[13] Pulmonary artery pressure and total pulmonary resistance have been noted to increase at rest and inordinately with exercise following beta blockade.[59, 73] Systemic arterial pressure may be slightly reduced.[15, 57, 75]

Experience in Cardiac Arrhythmias

Beta adrenergic blocking agents have now been used extensively in clinical trials for cardiac arrhythmias. These agents have been uniformly effective in arrhythmias in which catecholamines or digitalis are implicated and have been particularly effective in arrhythmias that have not been controlled by conventional therapy. The experience with beta adrenergic blockade in various cardiac arrhythmias is summarized in the following paragraphs.

SUPRAVENTRICULAR ARRHYTHMIAS. In supraventricular arrhythmias, beta blockade exerts a major pharmacologic effect by markedly increasing the refractoriness of A-V conduction. In almost all patients with atrial fibrillation the ventricular rate has been slowed. Reversion to sinus rhythm rarely occurs, and these agents usually are not effective in long-term maintenance of sinus rhythm.[8, 10, 28, 53, 54, 63, 66, 69] It is noteworthy that the beta blocking agents markedly potentiate the ventricular slowing induced by digitalis and that the combined use of these drugs is particularly efficacious in patients resistant or intolerant to digitalis. Beta blockade has been less effective in atrial flutter than in atrial fibrillation.[8, 28, 54, 62] The ventricular rate is frequently reduced and the flutter rate may be diminished, but these responses are not consistent. Paroxysmal supraventricular arrhythmias of all forms have been adequately controlled by beta blockade.[8, 26, 62] In many instances the paroxysms have been abolished or when they have recurred the ventricular rate has been slower and the paroxysms have been of shorter duration. In addition arrhythmias due to the Wolff-Parkinson-White syndrome have been treated satisfactorily.[26, 62] Supraventricular arrhythmias resulting from digitalis toxicity, particularly atrial tachycardia with block, uniformly have been controlled by beta adrenergic blockade. Invariably the ventricular rate is slowed, oftentimes the atrial rate is slowed and frequently normal sinus rhythm is restored.[8, 63, 66, 67, 70] Inordinately rapid sinus tachycardia has been effectively controlled in a number of instances.[28, 54, 66] Atrial premature contractions have been reduced or abolished by propranolol, but the effectiveness in this ar-

rhythmia depends, in general, on the contribution of sympathetic influences.[8, 63]

VENTRICULAR ARRHYTHMIAS. Beta blocking agents have been used in a variety of ventricular arrhythmias, with variable results. Ventricular premature contractions are controlled best when they are secondary to digitalis administration,[8, 10, 53, 54, 62, 66, 67, 70] myocardial ischemia, idiopathic myocardial hypertrophy[26] or the administration of anesthetic agents.[8, 49] Ventricular premature contractions occurring without obvious cause in reasonably healthy people have not been uniformly controlled.[8, 53] The results in ventricular tachycardia depend upon the etiology but in general have been more satisfactory in the paroxysmal than the sustained form.[8, 26, 63, 66] In ventricular tachycardia sinus rhythm may be restored, the ventricular rate may be slowed or paroxysms may be averted.[8, 26, 66] In several patients repeated episodes of ventricular fibrillation, uncontrolled by other methods, have been abolished by intravenous propranolol.[10, 58]

Toxicity

CARDIOVASCULAR TOXICITY. The beta blocking agents reduce the contractility of the myocardium and uniformly result in a decrease in cardiac output. In patients with congestive heart failure in whom myocardial catecholamines are probably reduced or depleted, propranolol may induce or potentiate heart failure.[8, 19, 54, 70] The reduction in ventricular function by beta blockade may result in a change in the urinary sodium excretion patterns. In normal persons and patients with mild heart disease, the diurnal patterns of sodium excretion may be altered so that a greater proportion of sodium is excreted during the night and early morning hours, although no change occurs in total sodium excretion. In patients with advanced heart failure, sodium excretion patterns may be altered so that there is marked sodium retention and fluid retention.[20]

A number of instances of deterioration of the cardiovascular status following beta blockade have been reviewed recently by Stephen.[61] Sudden death has been reported after the intravenous administration of these agents, but in most instances the patients were severely ill and the drug was given as a last resort. Hypotension may be induced in patients on oral therapy or may occur shortly after intravenous administration and may be treated by vasopressors, or if less acute, by withdrawal of the drug or a reduction in dose. Bradycardia may result from either oral or intravenous therapy and usually can be controlled by parenteral atropine.[42] Partial heart block has been reported but disappears with withdrawal of the medication.[61] Increases in pulmonary vascular resistance and pulmonary artery pressure may accentuate right heart failure.[59, 73] It is generally agreed that patients with overt or impending heart failure should be given digitalis prior to or concomitantly with propranolol.

GENERAL TOXICITY. Extracardiovascular toxicity of beta blocking agents has been infrequent and has occurred in less than 2 per cent of the patients.[61] A peculiar feeling of lightheadedness, visual disturbances

including blurred vision and visual hallucinations, paresthesias and mental confusion have been observed. Nausea, vomiting and mild diarrhea may occur. Two cases of nonthrombocytopenic purpura and one case of thrombocytopenic purpura have been reported. A predictable side effect has occurred in patients with asthma or obstructive lung disease, in whom beta adrenergic blockade has reduced ventilatory function and flow rates due to its bronchoconstrictor effects.[41] When given to women in labor, propranolol has resulted in a decrease in uterine contractions, necessitating artificial delivery.[42] Aside from potent cardiovascular effects the beta adrenergic blocking agents block the release of glucose and free fatty acids induced by epinephrine.[40] Patients with insulin-induced hypoglycemia may not show the usual epinephrine-like effects of hypoglycemia, such as sweating, palpitations and tachycardia.[1] In addition, propranolol has possibly contributed to hypoglycemia in diabetic patients.[33] No consistent alterations have been found in the laboratory evaluation of renal or hepatic function.[61]

Clinical Indications

Propranolol is indicated in supraventricular arrhythmias uncontrolled by digitalis or where further increments in digitalis would approach significant toxicity (Table 1). A major indication is in those arrhythmias where digitalis excess may be implicated and cardiover-

Table 1. *Integrated Approach to Acute and Recurrent Cardiac Arrhythmias*

CLINICAL SITUATION	THERAPEUTIC CHOICES*	ROUTE OF ADMINISTRATION†	
		Oral	Parenteral
	SUPRAVENTRICULAR ARRHYTHMIAS		
Atrial flutter and fibrillation	Digitalis‡ and/or cardioversion¶	±	+
Atrial flutter and fibrillation poorly controlled by digitalis	Cardioversion¶		
	Propranolol	+	±
Regular supraventricular arrhythmias, not taking digitalis	Carotid massage		
	Vasopressors		
	Digitalis† or cardioversion¶	±	+
	DPH (Diphenylhydantoin)	−	+
	Propranolol	±	+
Paroxysmal supraventricular arrhythmias, with or without digitalis, prophylaxis	Procainamide or quinidine	+	±
	DPH	+	±
	Propranolol	+	±
Digitalis toxicity; atrial tachycardia with or without block, nodal tachycardia, multiple premature beats	Potassium chloride with	±	+
	Propranolol	±	+
	DPH	−	+
	Procainamide or quinidine	±	+
Heart block and bradycardia from any cause	Depressant drugs contraindicated		

(Table continued on page 1229.)

Table 1. *Integrated Approach to Acute and Recurrent Cardiac Arrhythmias* (Continued)

CLINICAL SITUATION	THERAPEUTIC CHOICES*	ROUTE OF ADMINISTRATION†	
		Oral	Parenteral
	VENTRICULAR ARRHYTHMIAS		
Ventricular tachycardia associ-	Lidocaine	−	+
with surgery, myocardial in-	DPH	−	+
farction, etc.	Cardioversion¶		
	Procainamide or quinidine	−	+
	Propranolol	−	+
Ventricular tachycardia recur-	Procainamide or quinidine	+	±
rent, prophylaxis	DPH	+	±
	Propranolol	+	±
Ventricular premature beats, not	Procainamide or quinidine	+	−
taking digitalis, ambulatory, no	DPH	+	−
heart failure	Propranolol	+	−
Ventricular premature beats, not	Digitalis‡ with	±	+
taking digitalis, acutely ill,	Lidocaine	−	+
heart failure	Procainamide or quinidine	±	+
	DPH	−	+
Digitalis toxicity, premature	Potassium chloride with	+	±
beats, not acutely ill	Procainamide or quinidine	+	±
	Propranolol	+	±
	DPH	−	+
Digitalis toxicity, premature	Potassium chloride with	±	+
beats, ventricular tachycardia,	Lidocaine	−	+
acutely ill, heart failure	DPH	−	+
	Procainamide or quinidine	−	+
	Propranolol	−	+
Ventricular fibrillation	Electrical defibrillation with		
	Procainamide or quinidine	−	+
	DPH	−	+
	Lidocaine	−	+
	Propranolol	−	+

*In *relative* order of preference.

†+ Preferred route, depending on clinical situation; − do not use; ± optional route, depending on clinical situation.

‡Rapidly acting preparation.

¶Should always be preceded and followed by procainamide or quinidine.

sion accordingly contraindicated. It may be of primary benefit in patients with supraventricular or ventricular arrhythmias arising from anesthetic agents, exercise, myocardial ischemia, idiopathic myocardial hypertrophy or exogenously administered catecholamines, or when anxiety and tension play a prominent role. It should be used prophylactically for recurrent and paroxysmal arrhythmias only when more conventional agents have failed. Propranolol should not be given to patients with overt or impending heart failure before digitalization. The indications must be carefully weighed against the relative contraindi-

cations of heart failure, bradycardia and heart block, systemic hypotension, pulmonary hypertension or obstructive pulmonary disease.

Administration and Dosage

Propranolol may be given orally or intravenously. After oral administration there is good correlation between blood levels and the reduction in exercise tachycardia, although considerable variation in blood levels has been noted among individual patients. It is absorbed most readily in the fasting state and should be given prior to meals. Maximal effectiveness occurs one to four hours after oral administration and a measurable biological effect persists for five to six hours.[42] Orally, propranolol has been effective in arrhythmias in doses ranging from 30 to 120 mg. daily.[8, 26, 42, 66] It is advisable to start with 10 to 20 mg. three to four times daily and increase the dose as necessary. Blood levels do not appear to be cumulative, and there is no prolonged carry-over effect when oral administration is discontinued.[42]

Intravenously the maximal effect is usually noted within 10 minutes.[54] One to 5 mg. may be given at a rate of 1 mg. per minute,[42] although 0.5 mg. per minute may be a safer dose.[19] Slow administration is mandatory and once an alteration in rate or rhythm is noted the infusion should be discontinued.[42] Higher intravenous doses may be given, but only with extreme caution, and only when no side effects are observed with lower doses. A total dose of 10 mg. probably should not be exceeded.

The use of propranolol is currently restricted to approved clinical investigators.

Other Uses

The many potential uses for beta adrenergic blocking agents have been reviewed recently.[19] Propranolol hydrochloride has been found to be effective in a variety of clinical states in which catecholamines excess may be instrumental in symptomatology. It has been of significant benefit in patients with idiopathic hypertrophic subaortic stenosis, parkinsonian tremor, and in the management of the right ventricular outflow obstruction in tetralogy of Fallot. Theoretically these agents may be effective in controlling some of the manifestations of pheochromocytoma. Propranolol has been used in the treatment of various aspects of thyrotoxicosis but has proved effective only in control of atrial fibrillation. Its greatest clinical use may be in the long-term therapy of angina pectoris.

DIPHENYLHYDANTOIN

The clinical effectiveness of diphenylhydantoin (DPH) in epilepsy was well established before Harris and Kokernot[27] found that DPH was also effective in reducing the arrhythmias following experimentally induced myocardial infarction in dogs. Subsequently, sporadic reports occurred regarding the effectiveness of DPH in both experimentally induced and clinical arrhythmias.[36, 46, 55] Only since 1965 have there been numerous reports on the clinical applications of DPH in cardiac arrhythmias, and it has become an established part of the therapy of

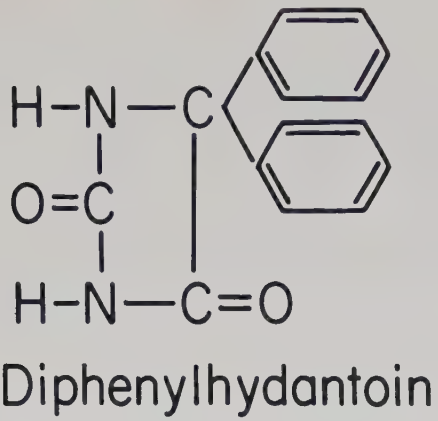


Figure 3.

these conditions. Concurrently, information has slowly accumulated on the cardiovascular pharmacology of this agent.

General Pharmacology

Structurally DPH is related to the barbiturates (Fig. 3). It is well known for its antiseizure activity without a corresponding reduction in central nervous system activity. DPH does not elevate the threshold for seizures, although a reduction in the voltage of electrical discharges and a decrease in their frequency have been noted. In general the action of DPH has consisted primarily of a stabilizing action against repetitive stimuli resulting in an "anti-spreading" effect from an area of abnormal discharge. The stabilizing effects of DPH have been shown to be common to all excitable membranes.[68] Chemically DPH has been shown to reduce the intracellular concentration of sodium in brain and in skeletal and cardiac muscle.[76] The exact mechanisms for the reduction in intracellular sodium have not been elucidated but may involve stimulation of the metabolically active sodium pump.

DPH is detoxified in the liver by hydroxylation of one methyl group and is excreted as the glucuronide in the bile or urine.[68]

Cardiovascular Pharmacology

The early animal investigations of DPH showed that it was effective in ventricular arrhythmias induced by experimental myocardial infarction or in atrial arrhythmias resulting from the application of aconitine or delphinine.[27, 55] In addition DPH was shown to be as effective as procainamide or quinidine in arrhythmias experimentally induced by digitalis.[46] In a number of instances DPH was found to reduce the frequency of ventricular arrhythmias, restore sinus rhythm or result in atrioventricular block. Recently a number of studies have been performed to more clearly delineate the cardiovascular pharmacology of this agent. In general the electrophysiologic mechanisms of DPH are similar to those of quinidine in that the conduction velocity between myocardial fibers is decreased.[18] DPH has been shown to shorten repolarization in the ventricle but not in the atrium and by shortening

the refractory period may be effective in cardiac arrhythmias by lessening the re-entry of ectopic impulses.[11] This may also explain why the drug is more effective in ventricular than in atrial arrhythmias. It has been well shown that the effects of DPH are due to its direct action on the myocardium and conduction system and not through its effects on reflexes originating in the central nervous system.[34] The most pronounced cardiovascular effect of DPH is direct myocardial depression. Myocardial contractility has been reduced by 25 per cent and central aortic pressure by 21 per cent when DPH is introduced directly into the central circulation. Associated with the decrease in contractility has been a rise in intraventricular pressures and a reduction in the maximal rate of rise of ventricular presure.[44] Ventricular function curves relating left ventricular diastolic pressure to stroke work and stroke power have shown a negative inotropic effect. Rapid administration has resulted in a more marked negative inotropic effect than slow injection, and repeated injections have produced a cumulative negative inotropic effect with pulsus alternans and cessation of effective ventricular ejection.[43] When DPH is injected into the isolated peripheral vasculature of experimental animals a direct vasodilating effect has been demonstrated.[44] There is evidence that DPH increases coronary flow and decreases coronary resistance, and thereby may be effective by improving myocardial perfusion.[24] A recent study in patients using clinical doses showed that DPH did not result in significant changes in cardiac output, peripheral resistance, or pulmonary vascular pressures.[16]

The effects of DPH on myocardial function and the peripheral vasculature are not unlike those observed for other antiarrhythmic agents such as quinidine or procainamide. In contrast, DPH seems to have a greater propensity for depressing the sinus node and for increasing A-V block, probably by directly increasing the refractoriness of conduction tissue.[14, 27, 46] The exact alterations in cellular metabolism of the myocardium have not been clearly delineated.

Experience in Cardiac Arrhythmias

In 1958, Leonard[36] first used DPH clinically in resistant ventricular tachycardia. Since then the drug has been used extensively in cardiac arrhythmias and its clinical indications are now reasonably well established.

SUPRAVENTRICULAR ARRHYTHMIAS. Intravenously, DPH has proved to be effective in a variety of supraventricular arrhythmias, although the responses are not consistently predictable. It has not reverted atrial fibrillation and atrial flutter to sinus rhythm, and has only rarely resulted in a transient increase in the A-V block in these arrhythmias.[14, 18, 47, 51] DPH has been effective in reverting atrial tachycardia to sinus rhythm.[14, 51] It has been noted to slow nodal tachycardias but has not been uniformly successful in reverting them to a sinus mechanism.[51] The drug has slowed the ventricular response in patients with digitalis-induced paroxysmal atrial tachycardia with block, and on occasions sinus rhythm has been re-established.[14] In a number of instances it has abolished or reduced the frequency of atrial premature

contractions.[14] Most investigators have found that DPH is primarily effective in supraventricular arrhythmias induced by digitalis.[14, 47, 51]

Orally, DPH has been successful in controlling recurrent cardiac arrhythmias resistant to conventional antiarrhythmic therapy. Paroxysmal atrial tachycardia, paroxysmal atrial fibrillation and premature atrial and nodal beats have been controlled satisfactorily.[9]

Ventricular Arrhythmias. DPH has been highly effective in controlling ventricular arrhythmias from many causes. It clearly has been most satisfactory in controlling bigeminal, sporadic or multifocal ventricular premature contractions resulting from digitalis excess.[14, 47, 51] In a number of instances, whether used initially or after other pharmacologic agents, it has reverted ventricular tachycardia to sinus rhythm.[14, 36, 47, 51] In one study DPH was utilized prophylactically in myocardial infarction and found to significantly reduce the number of ventricular arrhythmias when compared with a control group.[7] In addition, it has been utilized prophylactically to prevent ventricular fibrillation treated with direct-current countershock.[47] DPH has been effective intravenously in the control of ventricular arrhythmias resulting from cardiac surgery, cardiac catheterization, or cardioversion.[14, 47] Orally, DPH has resulted in long-term control of symptomatic ventricular premature contractions.[9]

Toxicity

Cardiovascular Toxicity. DPH depresses left ventricular function and results in vasodilatation,[43, 44] possibly to a lesser degree than quinidine and procainamide.[16] In addition, DPH depresses atrioventricular conduction and has resulted in high degrees of heart block.[14, 46, 51, 55] DPH also reduces the sinus rate and clinically has resulted in significant bradycardia with systemic hypotension.[14, 27] Cardiac and respiratory arrest may result after rapid intravenous administration.[27, 51] In these situations respiratory arrest may precede cardiac arrest.[27] The cardiovascular depressing effects of DPH depend not only on dose but also on the rapidity of administration, and doses that result in undesirable cardiac effects when administered rapidly may be tolerated well when administered over a longer period of time.[27] Sinus bradycardia or a high degree of atrioventricular block may be reversed rapidly with intravenous atropine.[14]

General Toxicity. Aside from its cardiovascular toxicity DPH has many noncardiovascular effects. Toxic effects have been noted in approximately 15 per cent of patients utilizing this agent.[9] DPH has been found in some patients to have cumulative effects, which do not become manifest until months or years after initiation of therapy. In some patients a familial deficiency of the hepatic enzymes that hydroxylate DPH has been demonstrated, resulting in a rapid accumulation of the active drug with resultant toxicity.[68] Adverse reactions include nervousness, ataxia, tremor, nystagmus, visual disturbances, gingival hyperplasia, pruritus, skin rashes, urticaria, depression, eosinophilia and arthralgias. Less common toxic manifestations include pancytopenia, megaloblastic anemia and an infectious mononucleosis-like syndrome.[60]

Clinical Indications

Intravenously DPH can be used in most situations where quinidine or procainamide is indicated (Table 1); it has the advantage of acting rapidly and having few adverse hemodynamic effects when administered appropriately. Although DPH has not been found to be effective in atrial fibrillation and flutter, it may be used in other regular or irregular supraventricular arrhythmias such as atrial and nodal tachycardias, multiple atrial premature contractions, and digitalis-induced atrial tachycardia with block, or wandering atrial pacemaker with tachycardia.

DPH is most effective against ventricular arrhythmias, particularly digitalis-induced premature contractions. It may be used primarily in ventricular tachycardia, or prophylactically in recurrent ventricular tachycardia or fibrillation.

Intravenous DPH is primarily indicated in arrhythmias presumed to be due to digitalis where cardioversion is relatively contraindicated. Its rapid onset of action makes it ideal in arrhythmias arising acutely during surgery or cardiac diagnostic procedures. It may prove to be of great benefit where the risk of hypotension limits the use of more familiar agents.

Oral DPH may be used as maintenance therapy in arrhythmias successfully reverted with intravenous administration. It may be given as a primary medication in recurrent supraventricular and ventricular arrhythmias including atrial flutter and fibrillation. Theoretically it may be effective in the recurrent arrhythmias arising as part of the Wolff-Parkinson-White syndrome. DPH is also indicated in patients intolerant to quinidine or procainamide and has the advantage of being effective in smaller dosage, making patient reliability a less critical factor.

Diphenylhydantoin is obviously contraindicated in bradycardia, or high degrees of heart block.

Administration and Dosage

DPH may be administered orally, intramuscularly, or intravenously. Intravenous DPH is usually effective within five minutes.[14] The duration of action of a single intravenous dose has not been adequately established, although detectable serum activity cannot be demonstrated after 24 hours.[68] Incremental doses have not been adequately evaluated, but it is the general impression that if beneficial effects are not observed with the initial dose, further doses will probably be ineffective. The selection of a pharmacologically effective yet nontoxic intravenous dose remains a point of major concern. Generally it is agreed that clinical doses should not exceed 5 to 10 mg./kg. and should be administered in a dilute solution in not less than five minutes and preferably in 10 to 15 minutes.[14, 18, 51] Lang et al.[35] report that a total dose of 15 mg./kg. may be safely tolerated when given over several hours. A convenient dose of 250 mg. given in five minutes is effective, predictable, and safe. The standard DPH solutions are highly alkaline and often result in significant pain along the course of the vein being used for

injection. Maintenance therapy of 200 to 400 mg. daily may be given orally or intramuscularly.

Used primarily as oral medication, DPH is given in a dose of 200 to 400 mg. daily. Following a single oral dose a maximal blood level is reached in eight hours. Administered chronically by the oral route it may take six to nine days to reach a stable serum level for any given dose.[68]

LIDOCAINE (XYLOCAINE)

Lidocaine (Xylocaine) is one of the most popular of the local and topical anesthetic agents. Compared with that of an equal concentrations of procaine, its action is more prompt, more intense, longer lasting and more extensive.[50] Lidocaine has been found to share the antiarrhythmic properties common to the local anesthetic agents and shares structural similarity with procainamide (Fig. 4). Sporadic reports have appeared in the past two decades referring to its effectiveness in cardiac arrhythmias, but only recently has it gained considerable acclaim as an effective agent. Lidocaine has now been used extensively in a variety of clinical situations, and many claims have been made regarding its effectiveness, but it has not been subjected to extensive clinical investigation. The experience with lidocaine has been limited to its use in ventricular arrhythmias.[29, 38]

Cardiovascular Pharmacology

Lidocaine shares the depressant properties on the myocardium common to all local anesthetic agents. This group of drugs has been found to decrease electrical excitability, conduction rate and contractile force. In addition these agents are potent arteriolar dilators.[50] Recently the cardiovascular effects of lidocaine have been compared with those of procainamide in two separate studies. Harrison et al.[29] tested the

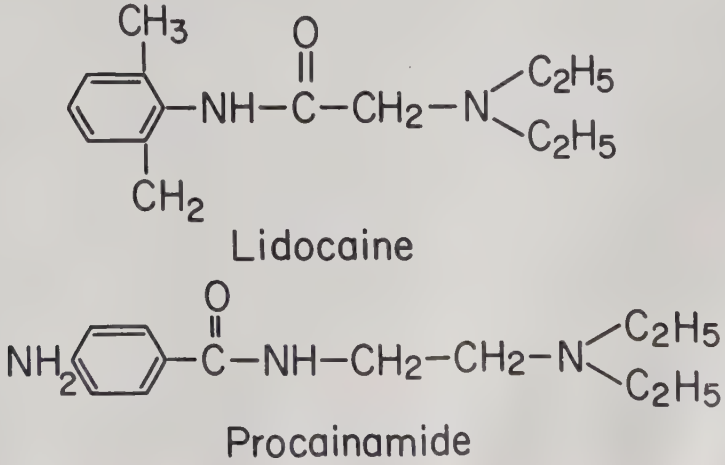


Figure 4.

effects of these agents in patients during cardiac surgery. Lidocaine in clinical doses was found to increase systolic blood pressure slightly without altering right ventricular contractile force. It was also found to increase diastolic threshold to electrical stimulation without altering the absolute refractory period. On the other hand procainamide in clinical doses resulted in a fall in systemic arterial pressure and a slightly greater fall in right ventricular contractile force. Its effect on diastolic threshold and the absolute refractory period was similar to that of lidocaine. Austen and Moran,[5] utilizing dogs with divided central and systemic circulations, found that lidocaine decreased myocardial contractile force at all drug levels while procainamide increased myocardial contractile force at moderate drug levels but depressed it at higher drug levels. Both agents proved to be potent peripheral vasodilators. When given into the systemic circuit both caused reflex diminution of myocardial contractile force, probably resulting from vasodilation and decreased cardiac work due to depression of the vasomotor center. Although the data are conflicting it appears that both lidocaine and procainamide have similar effects on ventricular function, with lidocaine showing greater antiarrhythmic potency at lower dosage.

Experience in Cardiac Arrhythmias

Lidocaine has been used exclusively in ventricular arrhythmias. In almost every instance it has corrected ventricular premature contractions, at least transiently, or reverted ventricular tachycardia to sinus rhythm.[23, 29] However, only a small percentage of patients have remained in sinus rhythm for prolonged periods of time.[29] Lidocaine has been highly effective in controlling ventricular tachycardia induced experimentally by digitalis.[32] It is noteworthy that in one study lidocaine was effective in all ventricular arrhythmias induced by digitalis while quinidine was effective in only 50 per cent of these arrhythmias.[23] Lidocaine is now being used successfully in coronary care units in the treatment of ventricular arrhythmias.[38] There is no information on the effectiveness of this drug in supraventricular arrhythmias.

Toxicity

Clinically significant hypotension, overt depression of myocardial function, high degrees of A-V block and significant bradycardia have not been reported with lidocaine. Idiosyncratic reactions have been reported with the intravenous administration of other local anesthetic agents—namely, central nervous system excitement, delirium, convulsions and sudden death. Such reactions have not occurred following the use of lidocaine in arrhythmias. On the other hand, drowsiness has been noted following its use for local anesthesia.[50]

Clinical Indications

Lidocaine currently is indicated in acute ventricular arrhythmias arising during the course of surgery or cardiac diagnostic procedures (Table 1). It has been successful in the treatment of ventricular ar-

rhythmias occurring in acute myocardial infarction and is probably the agent of choice in this situation. It is indicated initially in digitalis-induced ventricular arrhythmias or in other transient arrhythmias where potassium or slower acting drugs are necessary. It also may be useful in postcardioversion ventricular arrhythmias or prophylactically following successfully treated ventricular fibrillation. Other prophylactic uses may be in surgery prior to or during induction of anesthesia in patients with a propensity for ventricular arrhythmias. It also is indicated in vasopressor resistant hypotension in patients with ventricular arrhythmias.

Administration and Dosage

Lidocaine is administered intravenously and is usually effective in a dose averaging 1 mg./kg. The onset of action of lidocaine is prompt, usually in less than five minutes, and the duration of action of a single dose has been only 10 to 20 minutes.[22] Empirically 50 to 100 mg. are usually given rapidly and may be repeated every 10 to 20 minutes.[29, 38] General experience has shown that the dose should not exceed 500 to 750 mg./hour.[22, 29] In circumstances where the initial or repeated doses have been only transiently effective a continuous intravenous dose may be given for several hours at a rate of 1 to 2 mg./minute.[38]

The use of lidocaine for cardiac arrhythmias is currently restricted to approved clinical investigators.

SUMMARY

Three drugs, diphenylhydantoin (Dilantin), lidocaine (Xylocaine) and propranolol (Inderal), a beta sympathetic blocking agent, have proved to be effective in a variety of cardiac arrhythmias. The cardiovascular and antiarrhythmic effects of these agents are similar, and they depress myocardial function to variable degrees. They are generally indicated in acute or recurrent arrhythmias, and are particularly efficacious in arrhythmias due to digitalis toxicity. These agents generally do not replace quinidine or procainamide as maintenance therapy in chronic arrhythmias. Each is potentially toxic and must be reserved for fairly specific clinical situations. Table 1 summarizes a method for the integration of these drugs into the conventional therapy of acute and recurrent cardiac arrhythmias.

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Therapy in Coagulation Defects

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It should be axiomatic that improved diagnosis will be followed by improved therapy. Just as the coagulation scheme has become more involved and our diagnostic tests more specific over the years (Fig. 1), so too may our approach to therapy become more direct. No longer is fresh blood always the only or ultimate therapeutic tool. New drugs and components of whole blood are now utilized in specific situations and older therapies have found newer clinical purposes.

Hemorrhage may be due to (1) deficient synthesis, (2) increased rate of destruction or (3) inhibition of one or more coagulation factors.

Deficient Synthesis

1. Genetic abnormality: congenital deficiencies of coagulation factors I (fibrinogen), V (proaccelerin), VII (proconvertin), VIII (antihemophilic factor), IX (plasma thromboplastin component), X (Stuart-Prower factor), XI (plasma thromboplastin antecedent), XIII (fibrin stabilizing factor), von Willebrand's factor, platelets or some platelet factor.
2. Damage to the cellular site of synthesis: Liver disease deficiencies (II, V, VII, IX and X); bone marrow megakaryocytes (platelets).
3. Lack of available essential vitamin: vitamin K deficiency, administration of antivitamin K drugs (coumarins, etc.)—deficiencies of factors II (prothrombin), VII, IX and X.

Increased Destruction

4. Proteolytic (deficiencies of I, V, VIII; presence of a clot inhibitory fibrinogen breakdown product).
5. Intravascular coagulation (deficiencies of platelets, I, V, VIII±, II± presence of a clot inhibitor).
6. Combination of (4) and (5).

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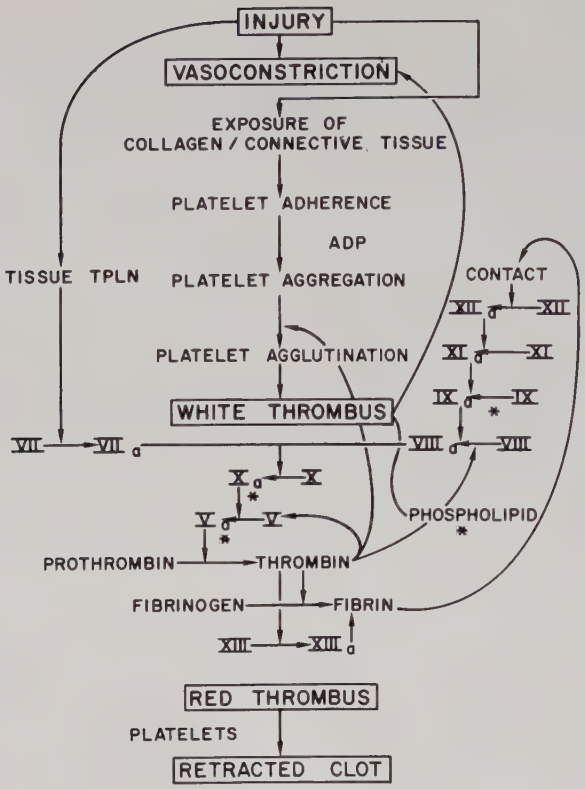

Figure 1.

PRESENCE OF AN INHIBITOR

7. Antibody which specifically inhibits one of the coagulation factors or platelets appearing as an autoimmune phenomenon or in response to infusions of a coagulation factor in a congenital defect.

Simple Deficiencies

Treatment consists of replacement of the missing factor or factors. Whole blood or plasma must be used unless specific plasma fractions are available. Hepatitis virus may be present in any blood product and its incidence is increased when a product is prepared from pooled plasma. Preparations listed below are available commercially or can be prepared by almost any blood bank. Other plasma fractions may be available but we are not clinically familiar with them.

Whole blood collected in plastic bags contains all of the coagulation factors. These are stable at 4° C. for at least 3 days and possibly longer. It is used when replacement of red cell as well as plasma volume is desirable.

Plasma preparations. (1) Fresh frozen plasma is stocked in most blood banks. ABO type specific plasma should be used and a minor

crossmatch is recommended. (2) Antihemophilic Plasma (Human) Dried (Hyland Laboratories) is lyophilized fresh frozen pooled plasma. Crossmatch is unnecessary unless large amounts are used.

Factor I (fibrinogen) preparations. Parenogen (Cutter Laboratories), Fibrinogen (Human) Dried (Hyland Laboratories) and Fibro-AHF (Merck, Sharp and Dohme) are lyophilized fractions of pooled plasma, high in fibrinogen, which are dissolved as directed and administered intravenously in dosage calculated to bring the plasma level to approximately 100 mg./100 ml. The plasma volume is estimated as 50 ml./kg. body weight. In simple fibrinogen deficiencies the half-life is about 4 days, and treatment should be repeated as necessary to obtain hemostasis and to maintain the fibrinogen level at 100 mg. per cent or above.

Factor VIII (antihemophilic factor). A number of investigations have explored various fractionation procedures in attempts to obtain fractions suitable for emergency and prophylactic treatment in hemophilia. Two of these are commercially available, one is prepared in the local blood bank and the last is under investigation. (1) Ethanol precipitate: Fibro-AHF (Merck, Sharp and Dohme). (2) Glycine precipitate: Antihemophilic Factor (Human) (Hyland Laboratories). (3) Cryoprecipitate, not available commercially but easily prepared in the blood bank by Pool's method.[1] (4) Polyethylene glycol precipitate, under development by the American National Red Cross.

Ideally the plasma level of factor VIII should be brought to 100 per cent but, as this is currently impractical, levels of 20 to 30 per cent are used in hemarthroses and 30 to 50 per cent in other types of hemorrhage or in preparation for surgery. As factor VIII has a relatively short biological half-life, a loading dose should be followed by maintenance doses every 4 hours for 48 hours, then every 6 or 8 hours as necessary. Such treatment is difficult with whole plasma, and circulation overload becomes a real problem. The fractions listed above vary considerably in their potency but all offer the advantage of decreased protein and fluid. Dosage is regulated by measurement of the recipient's factor VIII level, or, if this is impossible, the corrective effects on the serum prothrombin time or partial thromboplastin time may be used to estimate the efficiency of the treatment. Care should be taken that these fractions are administered promptly after reconstitution as they deteriorate on standing at room temperature.

In estimating the dosage, 1 gm. of Fibro AHF may be considered equivalent (in factor VIII) to 100 ml. fresh plasma, 1 vial of the Hyland fraction to 200 ml. and cryoprecipitate from 200 ml. plasma to 140 ml.

If clinical and laboratory response are not achieved the possibility of the presence of a circulating inhibitor (anti-VIII) should be entertained (see below for additional discussion).

For use of epsilon-aminocaproic acid in mucosal bleeding, see below.

Platelets. Preparations are (1) platelet-rich plasma (PRP), (prepared by centrifuging whole fresh ACD blood at 4000 rpm for 3 minutes and expressing the PRP into a sterile plastic bag, and (2) platelet concen-

trate, prepared by recentrifuging PRP at 5000 rpm for 5 minutes and expressing most of the supernatant platelet-poor plasma. The platelets are resuspended in 20 to 30 ml. of plasma.

Platelet transfusions are used for treatment of amegakaryocytic deficiencies (leukemia, etc.) and to control bleeding in thrombocytopathia. In our experience platelets from O^+ donors have been satisfactory. ACD in ordinary amounts is used despite occasional clumped appearance of the platelets in concentrates. This may be avoided by the use of additional ACD to lower the final pH. This maneuver decreases platelet clumping but if done directly to the whole blood will also decrease red cell viability.

Estimation of platelet quantity necessary for effective therapy may be made from the following approximate values. The level of platelets necessary for satisfactory hemostasis is 100,000 per cubic mm., a total of 100,000 minus the patient's pretransfusion count $\times$ 1000 $\times$ estimated blood volume (90 ml./kg. body weight). If we assume that the average donor's platelet count is 200,000 per cubic mm., that 70 per cent is the average recovery after differential centrifugation and that 70 per cent of these platelets will circulate in the recipient, 4.9×10^{10} platelets will be obtained from each 500 ml. unit of blood. Thus platelets from each unit of blood could be expected to cause a rise of only 10,000 per cubic mm. in an individual with a 5 liter blood volume. Platelet concentrates should be reserved for those patients in whom the plasma volume will be a problem, as they are only 60 to 80 per cent as effective a source of platelets as platelet-rich plasma. Repeated platelet transfusions may have decreasing effectiveness in control of bleeding.

As yet there is no practical, effective way to preserve platelet concentrates and prepare them rapidly for transfusion. Frozen glycerolized platelets have shown promise, and further research using agents such as dimethysulfoxide for preservation is in process.

Vitamin Deficiencies

Vitamin K is the only vitamin known to be essential to the synthesis of coagulation factors. Many excellent preparations have been available for some years. Vitamin K_1 preparations are efficacious in the treatment of coumarin intoxication and relatively safe in the treatment of newborn deficiencies (hemorrhagic disease of the newborn).

Fibrinolytic and Fibrinogenolytic Bleeding

Fibrinolysis is that state in which sufficient activator or fibrinolysin is present in or about a clot to cause its dissolution. Levels of fibrinogen and other coagulation factors in circulating blood may be normal. Fibrinogenolysis, on the other hand, is a much more profound disorder in which active fibrinolysis destroys circulating fibrinogen and factors V and VIII. Fibrinolysis is seen as a complication of liver disease, leukemia, carcinoma of the prostate, idiopathic thrombocytopenia and so forth, and if bleeding is a problem increased clot stability may be achieved by treatment with an enzyme inhibitor (EACA, see later).

Urinary tract bleeding, particularly postoperative, may be enhanced by the effects of urokinase (present in normal urine), which activates fibrinolysin, preventing the formation of stable hemostatic clots. Again treatment with EACA may be effective. Successful treatment has also been reported in oozing from the gastrointestinal tract and in some cases of menorrhagia. This inhibitor may also be effective in the control of mucosal bleeding (tooth extractions, hematuria) in hemophiliacs with or without additional plasma or fraction therapy.

Fibrinogenolysis is a rare and life-threatening complication often associated with some extensive surgical procedure or grave obstetrical complication. Postulated mechanisms include the introduction of activator materials into the circulation or a response to intravascular clotting (see later). In addition to destruction of fibrinogen, V and VIII, a fibrinogen breakdown product which is clot-inhibitory is found in the circulation. This material, called breakdown product D, is immunological, like fibrinogen, and acts as an inhibitor in the plasma-thrombin clotting time test. It is denatured by 5 minute incubation at 56° C., and this property is useful in differentiating fibrinogenolysis and intravascular clotting.

Treatment of fibrinolysis or fibrinogenolysis requires the use of an enzyme inhibitor; one such is currently available as aminocaproic acid (EACA; Amicar [Lederle Laboratories]). This is a monoamino carboxylic acid, structurally similar to lysine except for the lack of an alpha amino group. It acts mainly by competitively inhibiting profibrinolysin activators but may also inhibit fibrinolysin directly. It is excreted rapidly, largely unchanged in the urine. Gastrointestinal absorption is good and the drug can be given either intravenously or orally.

Effective blood levels are 13 mg./100 ml. or greater, which may be achieved in an average adult by a loading dose of 5.0 gm. and 1 gm. every 2 hours thereafter.

This inhibitor should not be used unless urinary output is adequate. It should be avoided in patients with cardiac or renal disease and with thrombophlebitis.

Intravascular Coagulation

Intravascular coagulation is a dynamic clinical situation in which the coagulation mechanism is triggered and clotting progresses with the consumption of various coagulation factors: platelets, fibrinogen, prothrombin, factors V and VIII. Fibrin so formed may be deposited in massive thromboses or diffusely in small vessels. Hemorrhage is secondary to the greatly diminished levels of these coagulation factors. Immediate treatment is imperative, but diagnosis is essential as the clinical picture resembles closely that seen in fibrinolytic bleeding. A low platelet count is an important differential test, as is the plasma-thrombin time. This may be prolonged due to the presence of a heat-stable inhibitor.

The first therapeutic aim is to stop the coagulation process and the second is to stop the hemorrhage. Heparin is the most effective anti-

coagulant and whole blood transfusions the most effective replacement for both coagulation factors and blood volume.

Heparin (commercially available from many sources) is an old standby but its usefulness for the therapy of bleeding has only recently been appreciated. Heparin is a mucopolysaccharide composed of glucosamine and glucuronic acid in the molecular ratio of 1:1 and differs from other mucopolysaccharides in that the sulfate groups are bound to amino groups to form sulfaminic linkages. The content of esterified sulfuric acid is very high, up to 40 per cent. It is the strongest organic acid found in the body. Heparin's anticoagulant activity may be related to sulfuric acid content. Hydrolysis of the ester linkage results in loss of this activity, and anticoagulant activity can be conferred on other high molecular weight polysaccarides by esterifying them with sulfate. The strongly acidic groups of heparin can be neutralized by free basic groups found in compounds such as protamine. The drug prevents clot propagation, causes prolongation of the whole blood clotting time, interferes with thromboplastin formation by preventing the activation of factor IX by activated factor XI, and in the presence of heparin cofactor (an alpha globulin) causes inhibition of the thrombin-fibrinogen interaction. It may also prevent platelet-thrombin interaction but is generally not effective in preventing ADP-induced platelet aggregation or platelet adhesiveness as measured by in vivo or in vitro techniques. Heparin plays a role in lipid clearance; what this means in terms of coagulation is difficult to evaluate.

Heparin should be administered intravenously in dosage sufficient to prolong the clotting time to approximately 30 minutes at 3 hours after the initial dose and repeated every 4 hours as necessary. In profound intravascular coagulation, no clot may be formed in the sample tube. In this case an arbitrary adult dose of 7500 USP units may be used. It is advisable to have protamine sulfate on hand as an antidote. Some inactivation occurs in the liver, but the drug is largely eliminated via the kidneys, and caution is necessary when there is impairment of glomerular filtration.

Combination of Intravascular Clotting and Fibrinolysis

This difficult situation may be encountered in many of the same circumstances in which fibrinolysis alone or intravascular coagulation alone are seen. Treatment must be carefully monitored. Agents to be used are heparin to stop intravascular clotting, blood to replace lost volume and coagulation factors, and finally EACA, but only if fibrinolysis persists.

Plasma fractions such as fibrinogen should be used for replacement therapy with considerable caution. If the initiating process is not controlled, fibrinogen infusion may only potentiate the hemorrhagic state, as more breakdown products will be formed.

Inhibitors

Both steroids and immunosuppresive agents have been utilized for therapy when specific coagulation factor inhibitors are present. Neither

have been impressively successful in terms of inhibitor elimination, although there have been a number of good clinical responses, particularly with the immunosuppresive agents.

In some types of thrombocytopenic purpura a platelet inhibitor can be demonstrated. Whether this is possible or not, about three fourths of the patients improve with steroid therapy. In those patients not responding, platelet transfusions may be beneficial; however, the platelet survival time is greatly shortened, and this treatment should be used only if there is actual bleeding.

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Drugs in the Treatment of Alcoholism

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The use of drugs in the treatment of alcoholism is dependent on two major considerations: the frame of reference within which alcoholism is conceptualized and the target points of the medication.

Alcoholism, unlike more specific entities the practitioner faces, does not lend itself to easy definition. For this writer alcoholism is a chronic behavioral disorder manifested by an undue *preoccupation* with alcohol and its use to the detriment of physical, emotional and social function. The emphasis in this definition is upon incapacity of function caused by preoccupation rather than amount, and the discussion of parameters of preoccupation and measures of impairment of function must be left for other places and other times. But the reader must be reminded that the approach, understanding, therapy and evaluation is holistic at all times, although for the purposes of this paper, specific symptom relief may be the theme of the moment.

The reader must bear in mind also the two target end-points of drug use in treating alcoholism: first, the drug treatment of the acute alcoholic state and the appearance of withdrawal symptoms at the end of heavy prolonged alcohol intake, and second, the use of drugs in the treatment and rehabilitation of the person afflicted with alcoholism once the acute manifestations of the chronic condition are no longer evident. In actual practice, however, to deal with the first state and not provide for the second is, in this writer's opinion, the poorest form of "half-practice," the height of therapeutic folly. Concern only for acute states permits practices which accomplish little beyond temporary relief and provides the potential for generous multiplication of this major physico-psychologico-social problem of alcoholism.

One other general point requires restating: no matter what the pharmacological action of a drug, one cannot completely evaluate its total effectiveness without knowing how, where, when and by whom the drug is provided and in what manner countervailing forces to its effect are present in the therapeutic situation.

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Patients who come or are brought to a physician or a hospital for treatment of an acute alcoholic state are in a most unhappy condition. Dependent upon the degree of disability, they are often anxious of mind and tremulous of body. Observation of their physical condition will reveal a mode of dress below their usual standard of neatness, body perspiring and cold, hair uncombed, face blotchy, eyes red, mouth dry, breath foul with ethanol odor, limbs tremulous, and signs and symptoms of anxiety. Depression of motor responses and affect are common, as well as expressions of guilt. This guilt is different from the guilt we psychiatrists ordinarily see because it is accompanied by overt evidence of "I have been a bad person," which is the way the patient and his society feel about an acute alcoholic bout requiring medical attention. Complicating this sorry state may be various physiological, traumatic or psychological symptoms of a lesser or greater variety, such as pneumonia or head injuries.

Depending upon the patient's station in life and the number of times he has appeared in this state before this physician or at that facility, he will be judged a fool or an alcoholic. In the former case he will be provided with mild medicants such as aspirin and perhaps a tranquilizer and sent home with a commiserating admonition; in the latter case, when he is treated (unfortunately, he often is not), a wide spectrum of medication is introduced along with a healthy helping of disgust and disapproval.

ACUTE ALCOHOLIC INTOXICATION

In the patient with acute alcoholic intoxication in whom careful examination reveals a not too profound toxic state, the patient may be treated with chlordiazepoxide (Librium), 10 to 25 mg. four times per day for one to three days without hospitalization. On the other hand, where the decision is to keep the patient under observation for a few hours, chlorpromazine (Thorazine) or other phenothiazines in doses of 10 to 25 mg. for one to three days may be employed.

CHLORDIAZEPOXIDE. Librium (chlordiazepoxide hydrochloride) is one of the more widely used medicants to lessen tension and anxiety in a variety of conditions. In the treatment of acute alcoholic states it has won its widest audience. Extensive drug studies suggest that it exerts its influence on the limbic system of the brain. Animal studies have shown a "taming" action with elimination of aggressive and fearful responses. These responses are produced without appreciable sedation (a desirable response in delirium tremens). Some authors[2, 6, 7, 14, 18] report effective reduction of the agitation common to chronic alcoholism, alcohol withdrawal states or in impending or actual delirium tremens. Most physicians use parenteral chlordiazepoxide hydrochloride with an initial dose of 50 to 100 mg. and follow this with repeated oral dosages to a maximum of 300 mg. per day. When the agitation is reduced, a maintenance dosage of 25 to 50 mg. three times per day may be used.

The physician should avoid using Librium in combination with potentiating compounds such as MAO inhibitors and the phenothiazine

group; in elderly alcoholic people, minimal doses are best used for maintenance, and other drug combinations—noted later—should be used. Precaution is also advised in the use of Librium in the suicidal alcoholic patient.

Although the evidence for toxic side effects is limited, syncope, drowsiness, ataxia and confusion have been reported.[6] Skin eruptions, idiopathic jaundice, menstrual irregularities, extrapyramidal symptoms and nausea have been associated with the use of Librium. It is advisable to procure liver function tests and blood counts when chlordiazepoxide hydrochloride is used as a medication over a prolonged time. Most of the adverse reactions can usually be controlled by reduced dosages or elimination of the drug without further difficulties.

D'Agostino and Schultz[18] reported upon the use of chlordiazepoxide in 300 patients with agitated alcoholic states. They found that in acute alcoholic intoxication there was a significant alleviation of aggression and agitation and a calming action leading to light sleep. They report complete clearing of hallucinations in acute alcoholic hallucinosis within 5 minutes of the intravenous administration of 100 mg. of the drug. The authors also found that an additional 100 mg. intravenously was necessary to eliminate gross, generalized tremors when these were present as the sole manifestation of alcoholic withdrawal. A repeated 100 mg. intravenously was necessary to control convulsions. Of interest is the finding reported by Short and Moore[32] that Librium was "more effective when the condition (alcoholic state) was uncomplicated by a major psychiatric disease."

Chlorpromazine. The chlorpromazine group of drugs effected the same revolution of care for the alcoholic that they provided for the chronically hospitalized mental patient. The ability of chlorpromazine to provide relief of tension and a calming effect without causing mental fogging or drowsiness is well known.[6, 11, 17, 27, 31] This calming or tranquilizing effect led to a host of derivatives commonly labeled "tranquilizers," but chlorpromazine remains most effective and most toxic. The sense of comfort that permits sleep in the acutely intoxicated alcoholic is enhanced by lessening of nausea and ease of eating much earlier. Anxiety is allayed, psychomotor agitation is diminished, and a more readily manageable patient is usual under chlorpromazine therapy.

Chlorpromazine may be administered at varying doses dependent upon the severity of the presenting symptoms, the stage of alcoholic withdrawal, and the complications involved. Its action is rapid. It can be administered intramuscularly or orally in doses ranging from 25 mg. to 100 mg. every 3 hours, while other clinicians use 100 mg. to 200 mg. doses by mouth every 3 hours until either agitation or confusion is eliminated or until the patient passes into sleep. For those patients who may be disoriented, confused, combative or suffering severe alcoholic gastritis, 50 mg. doses intramuscularly every 3 hours may be indicated.

Side effects of chlorpromazine and other phenothiazine derivatives are well known. Hypotensive responses, jaundice, dermatitis, agranulocytosis, dryness of the mouth, constipation and extrapyramidal symptoms have been reported as side effects. The appearance of jaundice

and agranulocytosis calls for the immediate cessation of use of the drug. Dermatological complications can usually be counteracted by the administration of a antihistaminic drug such as Benadryl (diphenhydramine hydrochloride), 50 mg. three times a day. The antihistaminic may be given concurrently with the phenothiazine without interfering with the latter's therapeutic effect. Extrapyramidal symptoms can be controlled by reducing the dosage and adding anti-parkinsonian medication, such as benztropine methanesulfonate, 2 to 6 mg. daily, without impairment of therapeutic efficacy. Reduction of dosage and bed rest will usually control the hypotensive and other side effects of chlorpromazine. The potentiation of depression must also be borne in mind in using phenothiazine derivatives.

The potentiating pharmacological action of chlorpromazine has led to the use of this medication extensively in combination with paraldehyde. Paraldehyde, in dosage of 12 ml. for the first dose, gradually reduced by 4 ml. every 6 hours, may be employed in combination with 25 to 50 mg. of chlorpromazine every 4 hours. This combination results in a synergistic action of great benefit to the patient. Sleep and calming is introduced quickly and easily with less need for protracted hospital care. Because limited dosages of each are used, the tendency to overmedicate is avoided and the best of both pharmacological worlds results. In our clinical experience side effects have been negligible and the potential for habituation diminished with a delineated medication schedule with limits set early.

Evaluation of results with chlorpromazine have for the most part been favorable. The trend now is to test more recent drugs and their effectiveness in the acute alcoholic state against chlorpromazine. One such study by Ban and his group[6] compared chlorpromazine and chlordiazepoxide in their relative effectiveness in preventing and treating alcohol withdrawal symptoms. The authors concluded that while both drugs were beneficial in controlling the alcohol withdrawal syndrome, chlorpromazine's effect was "more rapid and less erratic than that of chlordiazepoxide."

It should be understood that the use of drugs to control and prevent withdrawal symptoms in the acutely intoxicated individual does not preclude necessary ancillary measures, such as maintaining hydrostatic and electrolyte balances and providing adequate diet and vitamin supplements. Proper nursing care is essential as well as the medical management of other complications commonly associated with acute alcoholic bouts.

REHABILITATION

Most medical and other treatment facilities stop their efforts on behalf of alcoholic persons when recovery from the acute state has occurred. As we have shown,[13] the acute stage of alcoholic intoxication may be the crucial event in initiating a rehabilitative program for sufferers of alcoholism. Treatment of the acute stage of alcoholism alone is like pouring water into a sieve and being surprised when the floor is wet.

The total range of treatments available to alcoholic persons is not within the scope of this paper, except to say that any and all rehabilitative endeavors must be tailored to the individual needs of the patient and his resources. This requires a thorough evaluation of him physically, emotionally and socially. The use of drugs in the rehabilitation of the alcoholic person must be combined with a total effort in the patient's behalf. It is senseless to believe that by merely pushing some pills at a patient that an effective therapeutic response will occur. On the contrary, the correct interpretation by the patient will be one of disinterest and rejection by the physician and will only produce a potential addiction to some other drug.

To provide drugs in an effective manner in the rehabilitation of the alcoholic patient one must first have formed some sort of relationship. A practitioner who permits himself only a nodding acquaintance with his patient had better not try his hand at rehabilitating alcoholic persons. Interest, concern, respect and a desire to understand rather than judge are requisites of effective treatment. We must remember that alcohol is a drug—a central nervous system depressant—which the person uses in abundant doses as a form of self-medication. If we merely offer him another drug in an impersonal, disinterested way, we only increase the chances of his resorting similarly to misusing the new drug. The tailoring of medication to the patient in itself implies the necessity of learning something about the person, which is the cornerstone of beginning relations.

Different people have alcoholic problems for different reasons. Some are in physical or emotional pain; some are depressed and lonely; others are psychotic or fighting off psychotic disintegration. The possibilities are as numerous as the number of individuals.

Common to most alcoholic patients is the affect of depression.[19] The intense pain of aloneness and hopelessness that most alcoholic persons suffer does not lend itself easily to description. Suffice to say, though, the intensity is such as to demand relief at any cost. Reason and moralism cannot deal with what the person must contend with within himself and alcohol seems the sole solace; many are aware that, for some, alcohol only intensifies depression, but they cannot give it up because there is nothing else. Hence, since one goal of rehabilitation is the lessening or abolition of the need for alcohol, drugs which affect depression are one part of total treatment.

IMIPRAMINE. Imipramine (Tofranil) is an antidepressant which is a useful adjuvant in the treatment of alcoholic patients. The drug's action appears to be specific to depressive states; its effect has been characterized as depressolytic rather than stimulatory since, unlike iproniazid and amphetamines, it does not act by stimulation of the central nervous system. Although the mechanism of imipramine's action has not been established, evidence exists that it is not an inhibitor of monoamine oxidase.[5] Original investigators deduced that the etiological components of depression could be diminished by imipramine since it produces lowered blood pressure, decreased muscle tone, decreased reactivity to sensory stimuli and negligible sedative effect.[10]

Imipramine may be used for the wide range of depressions which are often seen associated with alcoholism from reactive types of depression to psychotic depressive states.[20, 21] Dosage range is usually 25 to 200 mg. daily, most usually administered orally, and 100 mg. is common as the average daily dose of imipramine. Signs of improvement or response to the medication may be measured by a number of criteria: disappearance of psychomotor inhibition, disappearance of feelings of hopelessness and helplessness, and lessening of self-destructive attitudes. Alcoholic patients often will report that with relief of depression by imipramine their desire for alcohol also diminishes. Imipramine is of further use in dealing with the rehabilitation of the alcoholic person in that there is a lessening of feelings of guilt. This helps the patient give up his anticipatory concept of hopelessness and helplessness. Furthermore, the alleviation of depression redirects the person from a preoccupation with his inner self to outer directedness, permitting the potential for reaching the patient with added rehabilitative methods. The amenability of patients, whose intense depression has been lessened, to respond to other measures is important. For some patients symptom control may be all that can be hoped for, while for others a drug-free life may be well within the reach of possibilities.

Side effects with imipramine are relatively infrequent and are usually readily controlled by a lowering of dosage. Dryness of the mouth, slight tremor of the extremities, dizziness and blurred vision, pruritus and dermatitis, nausea and vomiting are some of the side effects reported with imipramine. Rare cases of hypotension, exacerbation of eczema and ulcerative colitis have been reported.

Evaluation of clinical effectiveness has been favorable in the use of imipramine.[2, 3, 28, 36] Most investigators agree, however, that there is a certain delay before therapeutic effectiveness is noted and that the drug must be maintained for three months with gradual weaning over 10 days to prevent relapse. Some investigators feel that prolonged maintenance may be indicated, depending on the expected course of the depression.

Azima and Vispo[5] and Billig and Burris[10] report studies which demonstrate the effectiveness of imipramine in relieving depressive states. Our clinical experience at the Massachusetts General Hospital shows that imipramine is effective in lowering the intensity of the depression commonly found among alcoholic persons. In patients in whom imipramine is insufficiently effective, or in whom agitation accompanies depression, we have found amitriptyline hydrochloride (Elavil) useful.[1, 9, 24, 29]

AMITRIPTYLINE. Amitriptyline's principal effect is a slowing of spontaneous central nervous system electrical activity, resulting in brain wave activity similar to that in states of sedation. Large doses progressively diminish alerting responses to sensory stimuli. Potentiation of barbiturate effect is common with amitriptyline as is a significant degree of antihistaminic potential. Amitriptyline provides antidepressant and tranquilizing effects. The drug, therefore, may be used in depressions associated with alcoholism: manic-depressive reaction,

depressed phase; involutional melancholia; reactive depression; schizoaffective depressions; and neurotic depressive reactions.

Most patients respond to an initial dose of 25 mg. three times a day. Where more powerful doses are required, increments by 25 mg. may be used. A daily dose of 150 mg. is rarely exceeded. The expected response to therapeutic doses will require 3 to 30 days; 50 mg. per day is a common maintenance dose, which should be continued for 2 to 3 months after the alleviation of depression. In the event of relapse, reinstitution of amitriptyline hydrochloride is possible. Occasionally 2 or 3 ml. (20 to 30 mg.) may be injected intramuscularly to begin therapy.

Side effects are mild with amitriptyline. Drowsiness, dizziness, nausea, excitement, hypotension, tremulousness, weakness, headache, anorexia, perspiration and incoordination have been reported. Dermatitis and peripheral neuropathy have, in rare instances, been reported. High doses bring acute psychotic reactions as well as temporary confusion and disturbed concentration. Tachycardia, urinary retention, constipation and dry mouth sometimes appear with amitriptyline administration. Since the side effects appear to be an extension of the pharmacological activity of the drug, dosage reduction will usually suffice to control them. Use of the drug is contraindicated for patients with glaucoma and urinary retention. Furthermore, because of unpredictable potentiation effects, patients who have been receiving other antidepressants—especially those in the amine inhibitor group—should be allowed two weeks before amitriptyline therapy is introduced, and even then, it should be done cautiously and gradually. Of course, in the use of antidepressant medication with alcoholism (as in other depressed states), one must be on guard for suicidal possibilities as the patient improves. The use of any drug in the treatment of alcoholism without the careful interest and observation of an interested physician may be the source of a fatal therapeutic encounter when *only* symptom removal is the goal. Studies report equal effectiveness with amitriptyline as with imipramine in alleviating the depressive symptoms associated with alcoholism.[4, 30, 36]

There are other drugs beyond those noted that can be of significant use in the rehabilitation of alcoholic persons. *Trifluoperazine* (Stelazine)[8] is useful in treating patients who have thought disorders associated with alcoholism.[8, 16] We have found that small doses of trifluoperazine in combination with chlorpromazine are effective in controlling psychotic disorganization and thought disturbances in alcoholism; 1 to 2 mg. of trifluoperazine twice a day may be used with 25 to 50 mg. of chlorpromazine three times a day. Most of the side effects and precautions reported in the discussion of chlorpromazine would apply in the handling of trifluoperazine.

DETERRENCE

No discussion of chemotherapy in the treatment of alcoholism would be complete without reference to the drugs designed to deter drinking. Much dramatic hope has been raised by their presence on the

scene by those who wish to worship at the altar of simple answers to complex problems. Deterrent drugs have been disappointing. When, however, they are placed in proper perspective, their aid in the total treatment of the alcoholic problem can be marked.

DISULFIRAM. Most experience as well as most hope rests with disulfiram [bis(diethylthiocarbamyl)disulfide], more commonly known as Antabuse.[3, 11, 12, 22, 23, 34, 35] This substance is relatively inert in the body under ordinary circumstances, but when alcohol is ingested, it interferes with the metabolism of alcohol. The metabolic disintegration of alcohol occurs through the slow but constant breakdown of alcohol into acetaldehyde, which in turn is rapidly broken down into acetic acid and ultimately to carbon dioxide and water. Through a complicated process of chemical and enzymatic action not fully understood, disulfiram delays the acetaldehyde breakdown stage, and this highly toxic product of alcohol metabolism rises in concentration in the blood.

Moments after ingestion of alcohol into the body of the individual who has taken disulfiram, a toxic reaction begins. A rapidly deepening, ever-spreading lobster-red color develops from the head downward: face, sclerae, upper limbs and chest. The intense redness is accompanied by a sensation of heat and the rising crescendo of a pounding headache. Headache is accompanied by feelings of constriction in the neck and an irritation of throat and trachea, resulting in spasms of coughing. All of these unpleasant happenings are joined by a sudden steep rise in blood pressure for about 30 minutes to a point of maximum intensity, when there is a precipitous drop of blood pressure, the onset of nausea and the replacement of redness by pallor. If enough alcohol has been taken, nausea turns to violent vomiting. Breathing is difficult and gasping, precordial pain simulating a coronary attack is present; a sense of uneasiness and fear of dying develops—so terrifying that many a patient has wished for what he feared. After the severe discomfort has extracted its due for 2 to 4 hours, the patient falls to sleep, ending the discomfort as well as the alcohol-disulfiram reaction.

Beyond these symptoms, others have been reported: dizziness, head pressure, blurred vision, air hunger, palpitations, numbness of hands and feet and insomnia.

When disulfiram was introduced it was believed that an "experience session" with the drug and alcohol would certainly "cure" the alcoholic person's desire for drink. Person after person was hustled off to hospital after hospital, begun on disulfiram, and then given his half ounce of whiskey. In time, however (and after some reported deaths from cardiac and respiratory failure), it was deemed an unnecessary and perhaps cruel experience for patients. Consequently, now the treating physician only describes the consequences and the occasional patient who tests out his disbelief does not usually require additional evidence.

When a patient has purposefully or accidentally undergone a disulfiram-alcohol reaction, treatment should be directed at placing the patient in shock position and providing generous amounts of ascorbic acid intravenously. To the unconscious patient, intramuscular caffeine

and sodium benzoate will be beneficial. Electrolytic balance can be maintained by dextrose and saline infusions and plasma and oxygen provided where indicated. Antihistamine medication is useful intramuscularly or intravenously. Most useful, in the uncomplicated reaction, is chlorpromazine in 50 to 100 mg. intramuscular dosage. The calming, restful sleep which it introduces produces a refreshed patient on awakening without the unhappy events a disulfiram-alcohol reaction can produce.

Side effects to disulfiram alone have been minimal. Some complain of fatigue or a mild impotence. Others occasionally develop mild dermatitis, malaise, headache or gastric distress, and a few have a characteristic "garlic odor" to the breath, but all in all, problems are few.

Some therapists caution against the patient with incipient psychosis, severe coronary disorder, cirrhosis of the liver, kidney disease, diabetes, pregnancy, asthma and epilepsy, but most practitioners who are confident of their relationship and understanding of the individual have used disulfiram with people in these categories with caution and without harm.

The administration of disulfiram is relatively easy. One 500 mg. tablet is administered daily upon arising for five days, 24 hours after the last drink, and then half a tablet (250 mg.) daily is used as a maintenance dose. We suggest routinizing the taking of disulfiram, preferably upon awakening. This eliminates a day of decision making. Some caretakers maintain patients on 125 mg. daily (1/4 of a tablet), but our experience proves this an unsatisfactory maintenance dose. Patients who are maintained on 500 mg. daily develop symptoms of polyneuritis. Patients who discontinue disulfiram are advised to wait at least four days and preferably for one week before resuming their alcohol intake.

Generally, the many articles of evaluation of disulfiram effectiveness have stressed its usefulness as ancillary to a total program of rehabilitation.

Metronidazole. Recent hope has been raised in the mass media about metronidazole (Flagyl) as a drug to keep the alcoholic person from his alcohol. Although metronidazole produces a mild disulfiram-like reaction when combined with alcohol, its main effect, according to its proponents, is to produce a rapid aversion to alcohol, a decreased tolerance effect ("a little goes a long way"), and a reduced compulsion to ingest alcohol. The pharmacological basis for these effects is unknown at present, although it is of more than passing interest that the alveolar air of subjects who have taken metronidazole and ethanol is acetaldehyde-free while the alveolar air of these same subjects with disulfiram and alcohol yields acetaldehyde.

All information available at this writing concerning metronidazole is based upon uncontrolled observations of clinical findings.[33] No serious toxic effects have been reported to date and even its enthusiastic proponents stress that "the degree of motivation present or induced by the therapist in continuing to take medication as prescribed is, of course, a major factor in the success or failure of management of the alcoholic."

To date, the early observations of metronidazole are interesting and may be promising but, nevertheless, are only in the investigative stage.

The physiological and pharmacological search for the "specifics" of alcoholism should go on. Those of us primarily in the psychological branches of medicine have searched for the specific alcoholic personality, only to find gross responses common to alcohol problems and other ills of man equally as well. New methods may provide refinements in biochemical and physiological understanding of gross variables, but the subtle inner, individual pattern of physiological as well as psychological response will continue to demand a variety of skills and treatments for alcohol problems. These will have to be tailored and tested to the afflicted individual in a total program of understanding and will include psychological and physiological diagnosis as well as evaluation of the effects of social and family influences. When a total evaluation and understanding evolves, the patient can be provided with a rehabilitative program, one part of which can provide temporary symptom relief of associated difficulties with alcohol problems. But the practitioner who believes that his patient can be helped by a more thorough treatment than symptom relief alone must always remember that, just as alcohol can provide a chemical defense against letting the helping world in, so can the drugs we freely and easily prescribe imprison our patients in their chemical fortresses against even more beneficial effects. The material in this paper must be viewed against this background.

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Oral Contraception

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In 1956 the clinical trials using oral gestogens for ovulatory supression for fertility control were begun in Puerto Rico. Since that time, these oral estrogens and progestogens have experienced a phenomenal success. In 1965 over 5 million women in the United States of America were utilizing oral contraceptives, and over 2.5 million women in the world population outside the United States were adopting this method of contraception.[44]

Initially, the major concern of physicians and patients was for the safety of the oral gestogens for fertility control. No patient heretofore had taken a daily tablet to alter the hormonal relationships of the body for the sole, elective purpose of contraception. Over the past ten years, the problem of safety versus hazard has been quite favorably resolved by these several million women taking these potent hormones, with virtually 100 per cent effectiveness and few untoward reactions.[32]

Since this subject was last considered in the *Medical Clinics of North America*, in March, 1964,[13] several new preparations have been introduced and marketed in the United States. The new drugs introduced have usually been of lowered dosage with fewer side effects and no reduction in efficacy. The newer agents are undergoing careful scrutiny while investigation of the earlier marketed products continues.

RATIONALE OF TREATMENT

It has long been known that progesterone and estrogen can inhibit ovulation, but since progesterone is absorbed with variable potency from the gastrointestinal tract and available estrogens would not suppress ovulation indefinitely at orally tolerated dosages, these were judged impractical.[18]

This situation was changed drastically by the introduction of potent ovulation-suppressing steroids that are orally ingested and metabolized.[24] The 19-nortestosterone derivatives and related compounds were

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introduced and shown to be predictably absorbed from the gastrointestinal tract. Ethynylestradiol and ethynylestradiol 3-methyl ether (or mestranol) were made available to complement these newly introduced progestogens, since one of the annoying problems of the use of progestogens alone was the instability of the endometrium, with resulting breakthrough acyclic genital bleeding. The addition of these synthetic estrogens gives stability to the endometrium. In addition it was found that the synthetic estrogens alone without progestogens can suppress ovulation predictably at doses easily tolerated by the patient.[14]

This has led to the introduction of two methods of ovulatory suppression utilizing oral gestogens. The first is the combination approach, combining an orally potent progestogen with a variable amount of synthetic estrogen. These tablets are given from the fifth day of the menstrual cycle to the twenty-fourth or twenty-fifth day.

The second method is sequential, using a synthetic estrogen for ovulatory suppression for 15 to 16 days, beginning on the fifth day of the menstrual cycle, followed by the estrogen combined with a progestogen for five to six days at the end of the treatment cycle to allow predictable withdrawal bleeding from endometrial shedding.

PHARMACOLOGY—MECHANISM OF ACTION

The sequential method of ovulatory suppression utilizes the estrogen's ability to suppress follicle-stimulating hormone (FSH).[42] Ethynylestradiol 0.1 mg. and mestranol 0.08 mg. predictably suppress FSH. Progestogens suppress luteinizing hormone (LH),[42] produce in the endometrium a pseudodeciduoid change (secretory exhaustion), and thicken the cervical mucus, making it impenetrable to sperm migration. The 19-nortestosterone progestins are metabolized in part to ethynylestradiol and some of their effect may be from the estrogen produced by metabolism.[6, 30] In newer lower-dose combination agents the amount of estrogen is increased and the amount of progestin decreased proportionately. Therefore these agents rely more and more on the estrogen for its ability to maintain a stable endometrium, and possibly change its pituitary suppressive mechanism; however, it appears that the combination agents at present doses still suppress LH.[42]

METHODS OF ADMINISTRATION—AVAILABLE COMPOUNDS

With the presently available compounds a patient takes her medication as outlined in Table 1. The manufacturers provide the agents in packages designed to simplify the program and avoid forgetfulness. Elimination of tablets, particularly in the early part of the medication cycle, may lead to breakthrough ovulation, and it also increases the rate of breakthrough, acyclic bleeding,[29] which is one of the more frequent reasons given by a patient for discontinuing this program.

Table 1. *Oral Contraceptive Preparations Currently Marketed in U.S.A.*

SEQUENTIAL THERAPY

PREPARATION	DAYS
Chlormadinone acetate (6-chloro-6-dehydro-17α-hydroxyprogesterone acetate) and mestranol (17α-ethynylestradiol-3-methyl ether) (C-Quens, Lilly):	
Mestranol 0.08 mg.	15
Mestranol 0.08 mg. + chlormadinone 2 mg.	5
Dimethisterone (6α-dimethyl-17α-ethynyl testosterone) and ethynylestradiol (Oracon, Mead Johnson):	
Ethynylestradiol 0.1 mg.	16
Ethynylestradiol 0.1 mg. + dimethisterone 2.5 mg.	5
Norethindrone (17α-ethynyl-19-nortestosterone) and mestranol (Ortho-Novum, Sq., Ortho):	
Mestranol 0.08 mg.	14
Mestranol 0.08 mg. + norethindrone 2 mg.	6

COMBINATION THERAPY

PROGESTOGEN		ESTROGEN	
Norethindrone (17α-ethynyl-19-nortestosterone) (Ortho-Novum, Ortho; Norinyl, Syntex)	2.0 mg.	Mestranol (17-ethynylestradiol-3-methyl ether)	0.1 mg.
Norethindrone acetate (Norlestrin, Parke, Davis)	2.5 mg.	Ethynylestradiol	0.05 mg.
Medroxyprogesterone acetate (6α-methyl-17α-hydroxy-progesterone acetate) (Provest, Upjohn)	10.0 mg.	Ethynylestradiol	0.05 mg.
Norethynodrel (17α-ethynyl-5 (10)-estrenolone. (Enovid, Searle)	2.5 mg.	Mestranol	0.1 mg.
Ethynodiol diacetate (17α-ethynyl-estrene 3β, 17β-diol-diacetate (Ovulen, Searle)	1.0 mg.	Mestranol	0.1 mg.

PHYSIOLOGICAL EFFECTS

EFFECTS ON REPRODUCTIVE ORGANS

Uterus-Endometrium

SEQUENTIAL. The immediate intense estrogen dosage causes a proliferative change. In the latter part of the cycle, when the progesto-

gen is added, the estrogen effect persists until the twenty-third to twenty-fifth day of the cycle, when the endometrium takes on a mixed or secretory appearance. There has been no evidence of either hyperplastic or hypoplastic change after prolonged usage.[29]

COMBINATION. Following ingestion of the combined agents, the appearance of the endometrial glands is rapidly transformed from that of the early secretory stage to one resembling secretory exhaustion or pseudodeciduoid change.[9, 35] After the medication is discontinued, there is a prompt change to normal.[16]

Uterus-Cervix

SEQUENTIAL. The high estrogen dosage early in the cycle causes hyperactivity of the cervical glands, which produce a clear odorless mucus. This is more noticeable during the first several cycles of therapy.[29]

COMBINATION. The cervical mucus is thickened and tenacious and the cervix appears cyanotic; this is consistent with the predominant progestin influence.[8]

EFFECT ON ENDOCRINE SYSTEM

Pituitary Gland

Aside from the effects described under Rationale of Therapy, it appears that total gonadotropin output is not altered by ingestion of oral gestogens. There is at present no suggestive evidence that the structural changes in the pituitary or hypothalamus result when oral contraceptives are used by women. Further studies in this area are indicated.[9, 44]

Thyroid Gland

The protein bound iodine is increased by oral gestogens; this is thought to be caused by increase of the thyroxin-binding globulin (TBG) by the estrogens. The increase in TBG does not seem progressive and is immediately reversible after the medication is discontinued.[28, 44]

Adrenal Cortex

There have been no clinical problems related to the effects of oral gestogens on the adrenal cortex. Some evidence suggests an increase in the function of the pituitary-adrenal axis, but corticoid hyperfunction has not been demonstrated. Some 17α-acetoxyprogesterones have been converted in vivo to substances with corticoid activity but this has not led to corticoid insufficiency. The cortex responds to stress effectively during treatment.[8, 9, 44]

Ovaries

Both types of oral contraceptives affect the ovary similarly. Its size is decreased, it appears inactive, and it resembles a postmenopausal ovary. Histologic study of ovaries of women taking gestogens shows

that there is no functioning corpus luteum; after prolonged treatment there is a decrease in follicle density of the ovary. There is no evidence suggesting that orally active gestogens cause genetic damage to the oocytes.[8, 9, 24, 44]

Vagina

SEQUENTIAL. The clear odorless cervical secretion is occasionally confused with leukorrhea from vaginitis. In practice, vaginitis does not occur more frequently in users than in nonusers.[29] The excellent cornification of the vaginal mucosa (Fig. 1*A*) reflects the predominant estrogen effect.

COMBINATION. Possibly because of the incomplete cornification of vaginal mucosa, vaginitis is more common with these preparations.[43, 45] Another factor may be the altered glucose metabolism reported with norethynodrel-mestranol. A cytological smear from a patient on cycle day 20 is shown in Figure 1*B*.

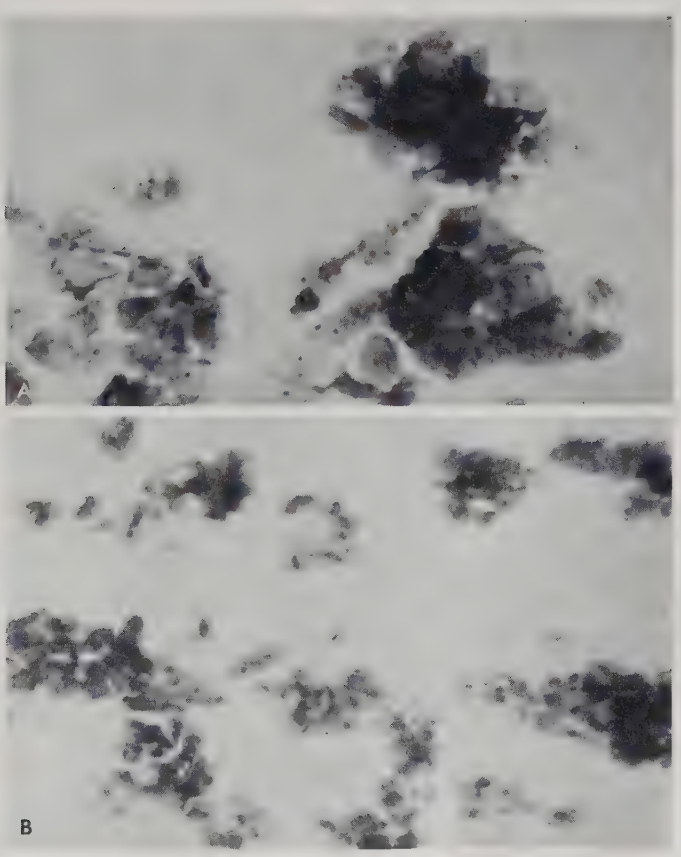

Figure 1. Vaginal cytology taken on cycle day 20. *A*, Sequential (C-Quens, mestranol and chlormadinone, Lilly), showing eosinophilic response. *B*, Combination (Provest, medroxyprogesterone acetate and ethynylestradiol, Upjohn), showing intermediate cell response.

Carbohydrate Metabolism

Although it has been suggested that the carbohydrate metabolism may be altered by the use of oral progestogens, no clear-cut evidence of an unexpectedly high frequency of abnormal glucose tolerance has been provided.[12, 44] Oral gestogens do not alter the severity of diabetes as measured by the insulin requirements. The development of diabetes has not been observed in large clinical studies and it may be inferred that the role of the oral gestogens in hastening frank diabetes in prediabetic women is probably less than that of pregnancy itself.[44]

Breasts

Neither sequential nor combination therapy changes the size of the breasts. No increase in the frequency of cancer of the breasts is apparent.[13, 44] The amount of lactation is decreased in approximately one of three lactating women taking oral contraceptives. Control data are lacking. It is unknown whether the excretion of oral gestogens in the maternal milk has an effect on the baby.

Menstrual Cycle

SEQUENTIAL. The cycle length becomes standardized, with cycles ranging between 26 and 29 days, and the flow usually mimics the patient's pretreatment pattern.[13, 29] Patients who previously had hypermenorrhea will also experience this on sequential medication.[29] Breakthrough bleeding occurs in 2 to 3 per cent of patients and is usually associated with tablet omission.[16, 29] Absent menses and missed menses are less common than with combination agents.[33]

COMBINATION. The cycle length variability is less with combination agents; cycles stabilize individually at 26 to 29 days. Withdrawal bleeding is less and missed menses is more common. The incidence of breakthrough bleeding is increased, particularly in the first cycles of treatment of with the agents with larger doses of progestin.[33]

OTHER SYSTEMIC EFFECTS

Liver

The storage of bromsulphalein sodium (BSP) is increased in the last trimester of pregnancy and during the administration of estrogens and certain C-17 alkylated steroids.

Large doses of oral contraceptives to rats and a few humans have caused alteration in the liver structure.[39] Although there has been no evidence of liver damage after long-time usage, these aspects continue to be studied.[16, 44]

Blood Coagulation

Thromboembolic disease in women has been found among users and nonusers of oral contraceptives. The Ad Hoc Committee for Evaluation of Possible Etiological Relationship with Thromboembolic Condi-

tions[1] was not able to establish statistically valid relationship between thromboembolic disease and the use of oral contraceptives.

Skin

Chloasma has been reported, particularly in dark-complexioned women. It may also be related to dietary and other environmental factors. The production of sebum may be decreased by oral gestogens, particularly those with more estrogen, and as a consequence acne improves.

Changes in Weight

Weight changes occur in 40 to 50 per cent of users of oral contraceptives; this has been reported by a large number of observers. The sequential and lower-dose combination agents are reported to cause far less variability.

Psychological Effects

Adequately controlled studies in this area are lacking. Forty randomly selected patients using mestranol and mestranol with chlormadinone acetate sequential underwent psychiatric evaluation in our office, and the indications are that the patients are generally psychologically comfortable while using oral contraceptives. Any fears about these agents (usually generated by lay magazine articles) are alleviated by reassurance and explanation by the physician prescribing the medication. Patients exhibiting overt depressive and anxiety reactions were found to have had similar pretreatment behavior problems. In general libido was not changed; however, the freedom from fear of pregnancy, when present in an otherwise mature interpersonal and intersexual relationship, enhanced the marital and sexual happiness.

EFFECTS ON SUBSEQUENT FERTILITY

Within three cycles after oral contraceptives are discontinued most patients return to normal cyclic bleeding and the endometrium returns to the pretreatment response pattern.[17, 25, 33, 34] Of 50 patients studied by the author, 48 were pregnant within six months. Of the two patients who had not conceived in six months, one was lost to follow-up and the other ovulated and conceived after administration of human menopausal gonadotropin.*

A careful gynecological history of patients who have difficulty with post-treatment acyclic bleeding and infertility may reveal that there was a similar pattern prior to treatment.

EFFECTIVENESS

The most important feature of a contraceptive agent is its effectiveness in use. Standardization of use effectiveness should be empha-

*HMG-ORTHO, Ortho Research Foundation, Raritan, New Jersey.

sized.[15] The most acceptable means of reporting effectiveness is in reference to 100 women years of exposure. The statistical significance of the pregnancy may vary depending on the number of cycles studied.

In Figure 2, the pregnancy rates and confidence limits of the sequential contraceptive, mestranol and mestranol with chlormadinone, are compared graphically with all published reports of combination agents, indicating similar curves of actual and confidence limit experience.[2, 5, 7, 10, 11, 16, 19–23, 26–28, 31, 36, 37, 40, 41]

A physician, then, may inform his patient that these agents will be effective if the directions for use are followed.

Failures, with breakthrough ovulation, occurred because of patient and medication failure. The early part of the cycle is the most sensitive, and for this reason, both the sequential and combination agents begin with their full dosage on the fifth cyclic day. Patients on sequential medication occasionally fail to begin the medication because of delayed onset of menses, which is related to the predominant estrogen characteristics of the endometrium. A patient taking a combination agent may similarly become confused because of secretory exhaustion of the endometrium, resulting in "silent" or "missed" menses. Patients should be cautioned to begin another medication cycle after seven days if menses have not interceded. Forgetfulness also causes difficulty.

Medication failure may occur in conditions that interfere with the absorption of the drug from the gastrointestinal tract, such as nausea, vomiting, diarrhea, and conflicting hormonal treatment.

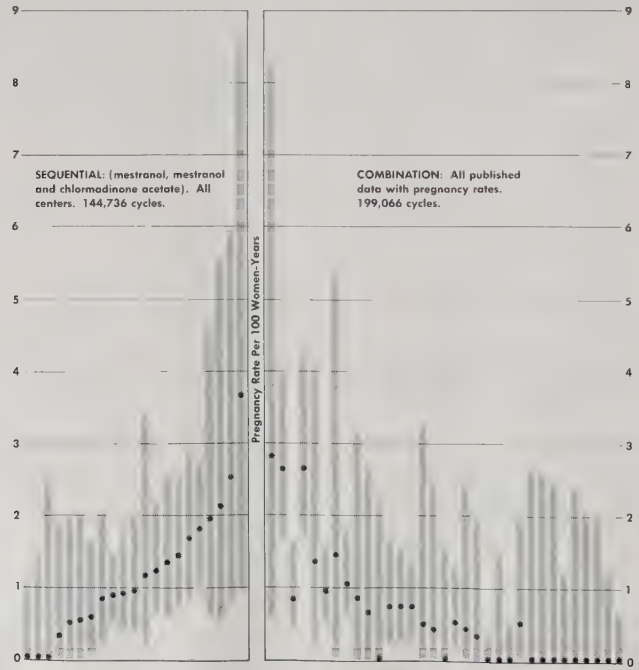

Figure 2. Use effectiveness of mestranol and mestranol with chlormadinone and compared with all published combination agents with applied 95 per cent confidence limits.

SIDE EFFECTS

As with use effectiveness, the reader and investigator must insert a measure of statistical significance to know whether a comparison of incidence figures is meaningful.[16] Table 2 is a comparison of clinical trials in a single clinic with confidence limits applied (Rice-Wray et al.).[16]

Of the side effects, nausea is probably the most common. This results from estrogen and is usually transitory, occurring in the first three cycles. Acyclic uterine bleeding, another commonly reported side effect, is also unusually transitory and appears most often in higher-dose combination agents. Its occurrence is increased by tablet omission and may be a measure of patient reliability as much as maintenance of endometrium. Missed menses, headache, mastalgia, and weight gain are also reported with all agents.

CANCER

Cancer of the Cervix

There is no evidence that the oral gestogens—either sequential or combination—alter cervical epithelium toward dysplasia or cancer. There is no increase in the frequency of atypical or suspicious cytological smears.[4, 25, 29]

Cancer of the Endometrium

Neither the sequential nor the combined therapy has shown any tendency to cause endometrial carcinoma. Endometrial biopsy data after prolonged use are incomplete, however.[9, 16, 44]

EFFECTS ON EXISTING GYNECOLOGICAL DISORDERS

A thorough history and evaluation is necessary to assess the gynecological disorder before oral contraceptives are prescribed because of the abilities of the agents to mask problems of endocrinopathy. Once the disorder has been diagnosed and evaluated, these gestogens may be used with favorable or occasionally unfavorable, results.

Dysmenorrhea

Both sequential and combination agents appear to give relief in primary dysmenorrhea, apparently by ovulatory suppression.[6, 29] A sequential agent (mestranol and mestranol with chlormadinone) has been reported to be slightly more effective in dysmenorrhea related to endometriosis.[3]

Acyclic Functional Bleeding

Both sequential and combination agents reduce the incidence of acyclic bleeding in patients who have the problem of an irregularly shedding endometrium. Since estrogens tend to increase endometrial stability and the sequential agents appear to have less breakthrough

Table 2. *Percentage Frequency of Side Effects**

		NUMBER OF PATIENTS	NAUSEA	BREAK-THROUGH BLEEDING	HEAD-ACHE	MISSED MENSES	DIZZI-NESS
1. Medroxyprogesterone acetate Ethynylestradiol	10 mg. 0.05 mg.	300	0.3	10.6 (7–14)	0.3	4.0 (2–6)	2.3 (1–5)
2. Norethindrone acetate Ethynylestradiol	3 mg. 0.05 mg.	1122	0.4	2.8	0.4	2.0	0.2
3. Chlormadinone Mestranol sequential	2 mg. 0.08 mg.	8638	2.4	2.1	2.5	1.6	1.4
4. Norethindrone Mestranol	2 mg. 0.1 mg.	3464	0.7	2.1	0.7	0.8	1.0
5. Ethynodrel diacetate Mestranol	1 mg. 0.1 mg.	2734	1.6	5.3	1.3	1.1	0.9
6. Norethynodrel Mestranol	2.5 mg. 0.1 mg.	409	2.2 (1–4)	2.0 (1–4)	0.2	1.5 (0.5–3)	2.4 (1–4)

*According to Goldzieher and Rice-Wray.[16] Binomial confidence limits are in parentheses.

bleeding in the early months of therapy, they may be immediately more helpful.

Oligomenorrhea

Patients who have lengthy cycles with little flow may be benefited by sequential medication for contraception, which in most patients causes a "normal" flow.

Hypermenorrhea

Patients in whom there is no apparent cause for hypermenorrhea would react most favorably to a combination agent since menses are generally reduced. In sequential treatment the menstrual flow is normal (72.9 per cent of patients), increased (16.6 per cent), or occasionally reduced (7.7 per cent).[29]

Leiomyomata

Leiomyomata would continue to grow with continuous hormonal treatment, particularly with estrogens, but no evidence has been shown that cyclic oral contraceptives effect appreciable growth of leiomyomata.[11]

RESUMPTION OF CYCLIC BLEEDING, OVULATION, AND FERTILITY AFTER DISCONTINUATION OF AGENTS

After the discontinuation of combination agents the first cycle is usually longer than average and may range from 28 to 36 days. This is not the case with the sequential agents. After the first cycle of treatment, the cycle returns to the patient's normal pattern and usually by the third cycle the endometrium is normal and ovulation occurs. Within three to six months a high percentage of patients who are otherwise fertile conceive.[1, 25, 33]

CHOICE OF AGENT

With the background of physiology, metabolism, and effects of these compounds, a direction for the choice of agent can be apparent after gynecological evaluation of the patient.[3]

Generally, the sequential and low-dose combination agents with proportionately larger doses of estrogen are tolerated well, have few unfavorable side effects, and are well accepted by the patient. In some instances, because of the character of the combination agent and its progestin-estrogen ratio, there are reasons for using some of the higher-dose combinations (Table 3).

AGENTS PRESENTLY UNDER INVESTIGATION

Combination

Mestranol 0.05 mg. with 1 mg. norethindrone* is soon to be marketed. Its clinical effectiveness is similar to that of other low-dosage combinations.

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*Norinyl 1 mg., Syntex Laboratories, Inc. Palo Alto, California; Ortho-Novum 1 mg., Ortho Pharmaceutical Co., Raritan, New Jersey.

Table 3. *Choice of Oral Contraceptive*

HISTORY	DESIRED EFFECT	TYPE		COMMENT
		SEQUENTIAL	COMBINATION	
Hypomenorrhea	Normal menses	×		
Hypermenorrhea	Less flow		×	Use combination with least estrogen, more progestin
Dysmenorrhea (primary)	Freedom from pain	×	×	Mestranol and mestranol and norethindrone sequential reported not as helpful
Dysmenorrhea (endometriosis)	Freedom from pain	×		Mestranol and mestranol and chlormadinine reported helpful
Hirsuties	No increased hair growth	×	×	Avoid 19-nortestosterone progestins
Mastodynia (estrogen-sensitive)	Relief of pain		×	Medroxyprogesterone combination because of its low estrogen and nonandrogenicity
Asthenia	Weight gain	×	×	Use 19-nortestosterone progestins
Acne	Clearing	×		Avoid 19-nortestosterone progestins; use more estrogen
Acyclic bleeding	None	×		Effective in first cycles
Vaginitis	None	×	×	Avoid norethynodrel
Gastrointestinal nausea	None	×	×	Use least amount of estrogen

Sequential

Mestranol 0.1 mg. for 14 days and mestranol 0.1 mg. with chlormadinone acetate 1.5 mg. for seven days dosage* may provide better ovulatory suppression than 0.080 mg. mestranol. The larger amount of chlormadinone over a longer period of time should allow more predictable endometrial shedding. A graduated sequential using ethynylestradiol 0.025 mg. seven days, 0.1 mg. ethynylestradiol 14 days, and 0.125 mg. ethynylestradiol with 10 mg. medroxyprogesterone for seven days† provides the convenience of uninterrupted continual therapy and, because of the graduation of estrogen dosage, reduces estrogen intoler-

*14 + 7 Eli Lilly & Company, Indianapolis, Indiana.
†Profem, The Upjohn Company, Kalamazoo, Michigan.

ance. There is a theoretical drawback since low dosages of ethynylestradiol have been shown to stimulate FSH and breakthrough ovulation might occur during the seven days of the 0.025 mg. ethynylestradiol.

Continuous Low-Dosage Progestogens[14]

The progestin chlormadinone acetate* in doses of 500 μg. caused breakthrough bleeding in about 20 per cent of patients but allowed no pregnancies in 945 women through 8091 cycles. Norethindrone† was used in 50 μg. doses; breakthrough bleeding occurred in 2.1 per cent of the women and 11 of 108 became pregnant. The mechanism of effectiveness of the preparations is not known but is probably due to antiestrogenic effects, changes in cervical mucus, and impaired sperm mobility.

SUMMARY

Since oral contraceptives were first introduced, over 5 million patients have begun using the medication with confidence in the efficacy and decreasing fear of the hazards. In the evaluation of hazards, individual response must not be overlooked, and when a problem presents, we must prove a cause-and-effect relationship, showing that the disease occurs more frequently among users of oral contraceptives than among nonusers. Isolated reports have failed to do this, although the value of early warning is not denied.

The various oral contraceptive preparations on the market today offer greater effectiveness than ever before. Each agent, chosen specifically after a consideration of the patient's past history, medical findings, and idiosyncrasies, can be prescribed with confidence that it will be satisfactorily tolerated and appreciated.

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*Lormin, Eli Lilly & Company, Indianapolis, Indiana.
†Norlutate, Parke, Davis & Company, Detroit, Michigan.

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The Clinical Use of Furosemide and Ethacrynic Acid

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The impressive developments that have occurred during the past decade in the continuing search for effective oral nonmercurial diuretic agents have produced benefits for the edematous patients that were unforeseen at the beginning of this search.[1–3] They have, however, created new problems in management of the electrolyte disturbances arising from diuretic use. Although these remarkable achievements began with a more or less systematic search for more potent carbonic anhydrase inhibitors, the new agents that have provided the greatest clinical benefit are without significant effect on carbonic anhydrase. Their principal pharmacologic action has been inhibition of sodium chloride reabsorption with a resulting marked sodium chloride diuresis and variable but frequently great loss of potassium in the urine. The two most recent additions to the list of oral nonmercurial agents, furosemide (Lasix; 4-chloro-N-[2-furylmethyl]-5-sulfamoylanthranilic acid) and ethacrynic acid (Edecrin; 2,3-dichloro-4-[2-methylenebutyryl]-phenoxyacetic acid), are much more potent than any previously available diuretics in either the nonmercurial or mercurial category.[4–6] The clinical experience already available indicates that these compounds will make a major contribution in the management of the most difficult edematous patients. As may be expected with such potent agents, it also appears that they are likely to produce serious electrolyte disturbances much more frequently than any of the other agents available. Their safe use in the management of edema requires an understanding of their pharmacologic actions as well as the mode of development of the electrolyte disturbances they are particularly likely to produce. The following presentation is concerned principally with these features of furosemide and ethacrynic acid.

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FUROSEMIDE

Furosemide, the newest of the sulfonamide diuretics, is the most potent of these agents by considerable margin. It is a relatively strong organic acid with a pK_a of about 3.8. It is quite water soluble and is rapidly absorbed after oral ingestion, its maximum effect occurring within the first hour after ingestion. The pattern of electrolyte excretion following exhibition of this drug indicates that its principal action is on sodium chloride transport; the increase in chloride excretion usually exceeds the increased sodium excretion that occurs following administration of the agent. Features regularly observed, both in the experimental animal and in man, include the excretion of nearly 40 per cent of the filtered sodium in the urine, a decrease in the ability to excrete ingested water (decreased C_{H_2O}), decreased ability to conserve water (decreased Tc_{H_2O}), increased hydrogen ion excretion, increased potassium excretion, and a decrease in the excretion of uric acid.[1, 8] Despite these striking changes in the rate of reabsorption of sodium chloride, no acute change in glomerular filtration rate results when the drug is given intravenously.[9] The striking clinical effectiveness of this drug has stimulated a very considerable investigative effort designed to elucidate its site and mechanism of action. Although numerous studies during the past two decades have dealt with the problem of localization of the site of action of diuretics within the kidney, significant progress in the unambiguous identification of the intrarenal site of action of diuretics has been made only relatively recently. Earley, Kahn, and Orloff[10] first demonstrated the usefulness of studying the influence of diuretics on the concentrating and diluting mechanism of the kidney as a means of identification of sites of action. These investigators recorded that chlorothiazide, when administered during water diuresis, reduced the rate at which solute free water (C_{H_2O}) was excreted. They were unable to demonstrate a comparable inhibition in water conservation when the drug was administered during hydropenia. On the basis of these data they concluded that chlorothiazide acted at the diluting site within the nephron, a region identified by micropuncture to include the ascending limb of the loop of Henle and the distal convoluted tubule. Seldin and co-workers, using similar techniques, were able to show that furosemide produced a similar but greater inhibition of solute free water excretion in hydrated animals. They reported that solute-free water conservation (Tc_{H_2O}) was also markedly inhibited by furosemide. On the basis of these two observations it was concluded that furosemide inhibits sodium transport in both the diluting and concentrating segments of the distal nephron. These studies therefore establish a site of action of furosemide that includes both the ascending limb of Henle's loop and the distal convolution. The question whether furosemide also exerts an inhibitory influence on sodium transport in the proximal convoluted tubule has been more difficult to answer. Micropuncture studies have yielded conflicting results.[12-15] It has been demonstrated, however, that when very large doses of furosemide are given to hydropenic experimental animals, the quantity of fluid reaching the distal

nephron increases to equal or exceed 70 per cent of the glomerular filtrate.[11] Since micropuncture studies have shown that normally 60 per cent of the glomerular filtrate is reabsorbed in the first two-thirds of the proximal convoluted tubule during hydropenia, this result can be explained only by postulating that substantial inhibition of proximal sodium reabsorption is responsible for the delivery of such large quantities of fluid to the distal nephron. It should be emphasized, however, that such results were obtained with very large doses of furosemide (100 mg. per kg. body weight) and it remains uncertain whether in the dosages usually used clinically, furosemide has any effect on the proximal nephron. Several studies have failed to show any depression of the hydrogen-linked or potassium-linked ion exchange mechanisms by this drug. It thus appears furosemide acts principally in the ascending limb of Henle's loop and distal convolution.

Clinical Use of Furosemide

Clinical experience presently available clearly establishes that furosemide is one of the most powerful diuretics currently available. Reports identify a natriuretic response with doses varying between 6.25 and 640 mg. daily.[16, 17] The magnitude of increase in sodium excretion is conditioned by a number of factors, including glomerular filtration, nature and severity of the disease requiring diuretics, and dosage schedule employed.[9] Highest doses have been used in cases of particularly severe heart failure and cirrhosis of the liver. With lowest doses (6.25 mg. given intravenously), however, the resulting increase in sodium excretion has been as great as 1.3 mEq. per minute.[16]

Furosemide is rapidly absorbed when taken orally and a maximal effect is usually observed within the first hour after oral administration. When it is given intravenously the peak diuresis also occurs during the first hour. With both oral and intravenous routes of administration, a single dose of furosemide increases sodium excretion about sixfold during this period.[16] This response can be increased by a sustained intravenous infusion. The duration of action following a single oral dose usually persists no longer than 6 to 7 hours. Furosemide will markedly enhance the maximum natriuresis established by hydrochlorothiazide but when the order of administration is reversed, hydrochlorothiazide is without effect on maximum furosemide diuresis. Since furosemide increases hydrogen ion excretion it may be expected that the effects of carbonic anhydrase inhibitors and furosemide would be additive, and this has been reported.[8]

Although, in a few instances, doses of 1800 mg. per day have been administered, the usual furosemide dosage necessary to produce a satisfactory diuresis is 20 to 80 mg. per day. The extraordinary potency of this drug requires that it should always be started in small doses and the dosage increased only after evaluation of the response to a small dose. Intermittent therapy is desirable to minimize the hazards of drug-induced electrolyte disturbances.

Exhibition of furosemide results primarily in sodium and chloride loss in the urine with loss of chloride usually exceeding that of sodium.[8]

Concomitant increases in urinary excretion of hydrogen and potassium ions indicate that the ion exchange mechanisms in the kidney are not inhibited. In heart failure, acute losses of potassium are generally of modest proportions. In general, potassium losses with furosemide, as with most of the other nonmercurial diuretics, are influenced largely by the presence and severity of secondary hyperaldosteronism. Since hyperaldosteronemia is less frequent and less severe in heart failure than in hepatic cirrhosis and nephrosis,[18, 19] it is not surprising that furosemide therapy is more likely to produce serious potassium losses in these latter two conditions.

ETHACRYNIC ACID

Ethacrynic acid is the most potent member of a new class of diuretic compounds reported by Schultz et al.[4] Its potency is comparable to that of furosemide and they are not additive (when either drug is administered following a maximally effective dosage of the other), a fact that suggests that they both act to inhibit the same transport site or sites within the renal tubule. This suggestion is borne out by data obtained by Goldberg[20] and Seldin[11] on the mechanism of action of ethacrynic acid. It impairs the concentrating ability of the kidney with resultant production of a nearly isotonic urine when given during hydropenia. It also partially inhibits excretion of solute free water during water diuresis. Thus, it inhibits sodium transport at both the diluting and concentrating sites of the distal nephron. Reports concerning its effect upon the proximal tubule are conflicting but it is probable that it has no significant action on the proximal tubule in the usual clinical dosage range.

Ethacrynic acid is rapidly absorbed and its peak action usually occurs within 60 to 90 minutes after ingestion.[4, 8] The pattern of electrolyte excretion following exhibition of this drug is similar to that seen with furosemide. Both sodium and chloride excretion increase markedly, the increase often exceeding 2 or more mEq. per minute. Chloride excretion usually exceeds sodium excretion; the difference is accounted for by increased excretion of titratable acid, ammonium ion, and potassium. Indeed, the magnitude of chloride loss following exhibition of ethacrynic acid is so great that acute alkalosis is produced quite regularly with higher doses of this agent. The alkalosis results from the removal of an approximately isotonic solution of sodium and chloride from the extracellular fluid, and the resultant shrinkage in the extracellular fluid without bicarbonate loss results in an increased bicarbonate concentration. This sequence of events has been termed "contraction alkalosis" by Laragh et al.[8]

Satisfactory diuresis in congestive heart failure and hepatic cirrhosis is usually produced by dosages of ethacrynic acid varying between 50 and 200 mg. daily. Much larger doses have been used with benefit in patients who are severely edematous and refractory to the usual dosages.[8] These larger doses should be used with caution, however, since they can easily result in severe acute sodium depletion. In renal disease, dosage is variable and larger doses should be used only with

great care because of the particular hazard of sodium depletion in these patients. This hazard is great for both ethacrynic acid and furosemide, but their judicious use in the presence of severe renal failure is not contraindicated.[9, 21]

ELECTROLYTE DISTURBANCES PRODUCED BY ETHACRYNIC ACID AND FUROSEMIDE

The remarkable potency of these drugs makes excessive diuresis or sodium depletion a particularly great hazard. Since they are capable of inhibiting tubular transport of sodium to a degree that permits approximately 50 per cent of filtered sodium to appear in the urine, acute sodium depletion can occur within a matter of hours. It is possible to produce cardiovascular collapse and death in experimental animals in 3 to 4 hours with large doses of either agent if sodium repletion is not effected.[13] The magnitude of the diuresis reported in man with large doses of either of these diuretics suggests that a similar response can be observed clinically if proper caution is not exercised. The problem is made more difficult by the variations in diuretic responsiveness exhibited by different patients.[8] It is thus imperative that initial therapeutic dosages of these compounds be small and increases in dosage be instituted only after the physician has had an opportunity to observe the response to smaller doses. Administration of between 25 and 50 mg. of either of these agents as an initial dose and gauging maintenance therapy on the response to this dose appears to be the safest means of initiating therapy. Careful watch should be kept for signs of sodium depletion, including weakness, lassitude, and in more advanced cases syncope on sitting up or standing.[22] These changes are associated with an increasing hematocrit and rising blood urea. Acute sodium depletion is usually readily corrected by temporary cessation of therapy and liberalization of sodium intake. Effective repletion can almost always be accomplished by the oral route.

Acute alkalosis is more commonly produced by these agents than is acute sodium depletion and is particularly hazardous in cirrhosis of the liver. The mechanism is primarily that of acute chloride depletion rather than potassium depletion and intracellular acidosis, but potassium depletion is a common sequel to prolonged therapy. The selective loss of sodium and chloride may produce marked alkalosis even before the patient is rendered edema-free. Since the combination of rapid chloride loss and increased hydrogen ion secretion are associated with a corresponding increase in bicarbonate reabsorption, it may be expected that acetazolamide or a similar agent would inhibit the development of alkalosis and at the same time serve as a more effective diuretic regimen.[8] In congestive heart failure this regimen is preferable to treatment of the alkalosis by ammonium chloride or lysine monohydrochloride. The hazard of acetazolamide administration in hepatic cirrhosis precludes the routine use of this combined regimen in this condition.

Potassium depletion is another common disturbance in patients

treated with either ethacrynic acid or furosemide. The magnitude of the increase in potassium excretion evoked by both drugs is conditioned by the natriuretic response and the level of aldosterone secretion.[8, 19] Since both diuretics under consideration here produce prompt rises in plasma renin, it is to be expected that hyperaldosteronism (secondary) regularly results from use of these diuretics. Thus continued use of either agent leads to increasing potassium losses. Hence, it is imperative that close watch be kept on the state of potassium balance when these agents are used, and during maintenance therapy potassium supplementation should always be used. Patients with a high sodium intake during treatment with either ethacrynic acid or furosemide are particularly likely to develop severe potassium deficits. In such patients, large doses of supplemental potassium may be required to maintain potassium balance. Because of the marked tendency to develop hypochloremia during treatment with either ethacrynic acid or furosemide, potassium chloride should be used in replacement therapy.

The effectiveness of these agents in treatment of the dilutional hyponatremia that frequently complicates severe congestive heart failure and hepatic cirrhosis has not been adequately evaluated. Preliminary observations suggest that they may on occasion produce a remarkable diuresis and promote loss of water in excess of solute, despite the fact that high doses of either agent will regularly depress free water clearance (C_{H_2O}).[8, 22] In some instances, however, they are incapable of producing a diuresis in patients with severe heart failure and dilutional hyponatremia. Definition of the optimum usage of these drugs in management of this severe therapeutic problem must await further study.

Drug toxicity has not been a significant problem in the studies thus far reported with either furosemide or ethacrynic acid. It may be anticipated that drug hypersensitivity in any of its forms will be seen with either drug but present reports would suggest that these problems will be no greater with either of these new drugs than with other currently used diuretics. Hyperuricemia occurs regularly during the course of sustained oral therapy with either agent.[8]

SUMMARY

Furosemide and ethacrynic acid are new diuretic agents that exhibit a much greater natriuretic potency than any other diuretics currently available for clinical use. Both agents produce natriuresis and chloruresis in the usual pharmacologic doses, accompanied by increase in excretion of hydrogen and potassium ions. Their principal sites of action appear to be on sodium transport at the concentrating and diluting sites of the distal nephrons. Because of their extraordinary potency, they are particularly prone to produce clinically significant electrolyte disturbances. To minimize these hazards, therapy is best initiated during a period of hospitalization and continued after ambulation only when careful observation has identified the dose-response characteristics of the drug in the particular patient under therapy. Intermittent therapy is preferable if the patient can be maintained edema-free by this means.

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Low Molecular Weight Dextran

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In the last decade much interest has been focused upon low molecular weight dextran,[24, 98, 99, 103] and many experiments have been designed to delineate its mechanisms of action and clinical applications. Investigation of the properties of dextran has made possible extension of its use beyond its original application as a plasma expander. A brief review of the historical aspects, the pharmacology, the mechanisms of action, the toxicity and contraindications, and the clinical uses and efficacy of low molecular weight dextran follows.

HISTORICAL ASPECTS

In 1863, colloidal solutions were used experimentally as plasma substitutes by Ludwig when he perfused a pig's kidney with a 3 per cent solution of gum arabic. Interest in the physical properties of the suspension fluid of human blood led Starling, in 1896, to the conclusion that the colloids in the suspension fluid were basic to intravascular fluid circulation and retention. During World War I, Hogan's gelatin solution or gum saline was administered to the wounded and provided much information about the therapeutic possibilities of colloidal solutions. In 1942, Ingelman observed that the bacterium Leuconostoc mesenteroides polymerized the glucose of sugar beet into a molecular colloid. In subsequent experimentation, Grönwall and Ingelman[51] produced solutions of smaller molecular size which could be given to patients. In March, 1944, Thorsén[101] of Sweden reported the administration of dextran to patients for the first time.

Thorsén and Hint[102] continued to analyze the mechanisms of action of dextran upon the suspension stability of blood. As the molecular weight of dextran decreased, cell aggregation was further influenced and the term *low molceular weight dextran* was introduced (molecular weight less than 60,000).[42] In 1948, Bloom independently prepared the

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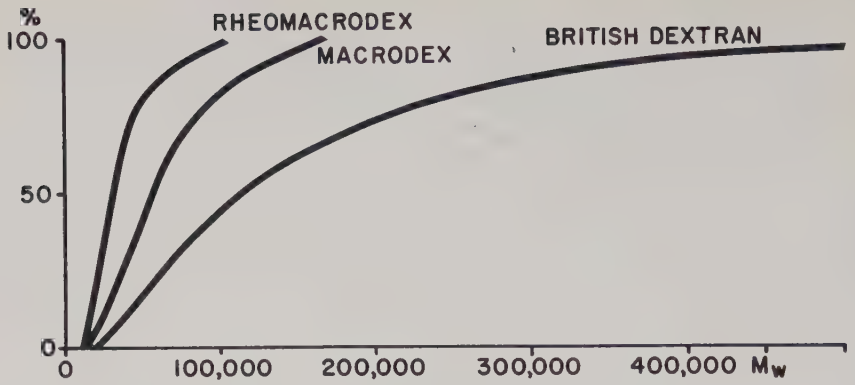

Figure 1. Molecular weight distribution of different dextrans.

first American dextran.[18] During the Korean War, it was widely and successfully used as a nonbiologic colloidal solution for treatment of conditions associated with a decreased blood volume.[6]

Gelin[39] provided great impetus to the study of low molecular weight dextran when he reemphasized that anemia after major trauma was greatly influenced by the sequestration of aggregated erythrocytes in the microcirculation. Low molecular weight dextran was observed to alter the microcirculation, and the effects of various fractions of dextran upon the microvasculature have been the subject of thorough investigation.[11, 12, 44] Renewed interest in the microvasculature has prompted much interest in the concept of "blood sludging." Attention was focused upon the microvasculature by Knisely and associates[60-62] in 1942, but it remained for the unusual properties of low molecular weight dextran to stimulate further investigation of blood sludging.[104] Currently three forms of dextran are available: low molecular weight dextran with an average molecular weight of 40,000; commercial American dextran with an average molecular weight of 75,000; and British dextran with a molecular weight of 150,000 (used only for experimental production of cell aggregation) (Fig. 1).

PHARMACOLOGY

The polysaccharide dextran is an anhydroglucose polymer produced by various strains of the bacterium Leuconostoc mesenteroides. The formula is:

$$\text{N sucrose} \xrightarrow[\uparrow \text{dextran sucrose}]{} \text{dextran} + \text{N fructose}$$

The majority of bonds linking the glucose units are of the α 1 to 6 types (Fig. 2). The native dextran demonstrates a high degree of branching with a high molecular weight with a mixture of molecules of different

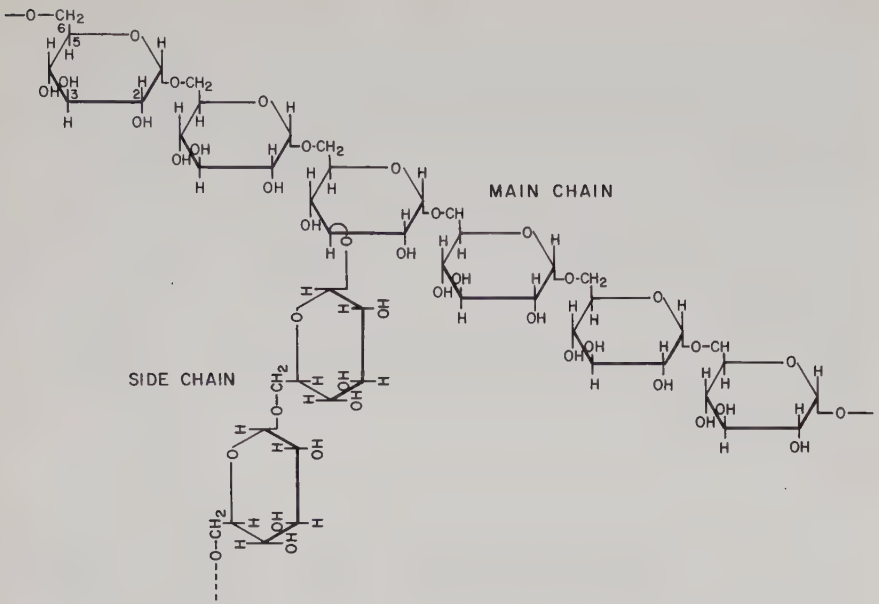

Figure 2. Structural formula of dextran.

chain links. This same product contains molecules of molecular weight from hundreds of millions to only a few glucose units.[43] Low molecular weight dextran is formed by a process of partial acid hydrolysis and fractionations. The average molecular weight is approximately 40,000 and the intrinsic viscosity is about 0.19. Ninety per cent of the molecular weight distribution of low molecular weight dextran is between 10,000 and 80,000. Ten per cent solutions in normal saline or in 5 per cent dex-

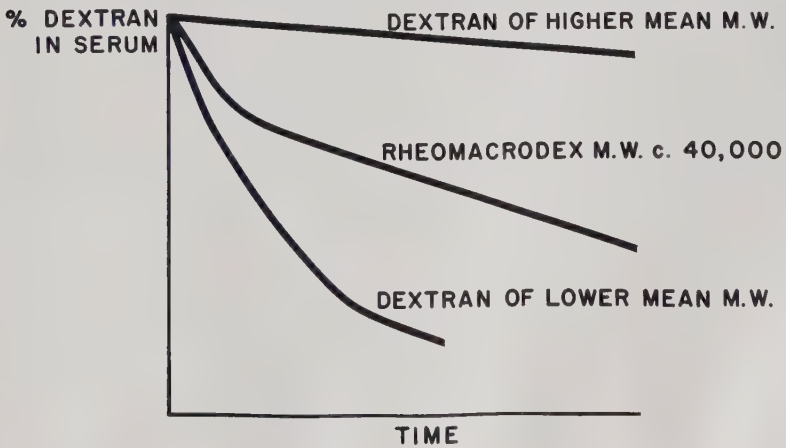

Figure 3. Plasma concentration of dextran solutions.

trose and water are available for clinical purposes. The colloidal osmolality is approximately 2.5 milliosmols per liter.

The plasma-expanding effect of dextran depends upon the colloidal osmotic characteristics and is a function of the molecular size concentration and the membrane characteristics of the general capillary bed.[4] The duration of influence by low molecular weight dextran is a function of the time that dextran remains in the circulation. There is rapid loss of the smallest molecules in the urine. Approximately 55 per cent is excreted within the first four hours after infusion, and from 60 per cent to 90 per cent within 12 hours.[3] A small number of the dextran molecules will equilibrate in the extravascular compartment, as the renal threshold for dextran is 50,000.[5] Storage occurs in the reticular epithelial system for a few days, and finally the polymer is slowly metabolized by dextran-degrading enzymes to carbon dioxide and water.

MECHANISMS OF ACTION

The role of the microcirculation (in vessels with an internal diameter of 100 μ or less) in certain shock states is a subject of considerable interest.[21, 22] Earlier studies of Knisely and associates and present studies emphasize the primary role of erythrocyte aggregation in microcirculatory flow abnormalities.[46, 53, 109] The non-newtonian characteristics of blood under conditions of low flow rate and high viscosity have been analyzed by means of the Couette viscometer.[28, 47, 110] Studies indicate that as the shear rate of blood approaches zero, a sludging occurs and the viscosity of the blood increases. Intravascular hemagglutination and capillary stasis are significant aspects of the microcirculation in severe shock states. Low molecular weight dextran has been shown to reduce the visibly intravascular cellular aggregation in animals and in humans.[41, 49, 69, 97] Infusion speeds the microvascular flow both in the capillary venules and in the arteriolar capillaries, and tissue perfusion is improved.[95] When low molecular weight dextran was given to humans with elevated sedimentation rates, plethysmographic studies revealed an increase in peripheral blood flow.[40] Lepley and associates[70] demonstrated the protection offered the microvasculature by low molecular weight dextran given to dogs after a 60 per cent decrease in blood volume.

Shoemaker[94] has shown the value of low molecular weight dextran in inhibiting or reversing erythrocyte aggregation after shock or thermal injury. Low molecular weight dextran exerts its greatest effect upon the peripheral circulation when there is impairment by erythrocyte aggregation or by diminished perfusion pressures. Venous flow is improved; the hematocrit value is lowered; the blood volume is increased; and the viscosity is decreased with the administration of low molecular weight dextran.[91, 93] The maximum desludging effect occurs after infusions of dextran of molecular weights of from 22,000 to 40,000.[89]

The mechanisms by which low molecular weight dextran exerts its influence upon the microcirculation are intimately associated with

the pathophysiology of erythrocyte aggregation. Fåhraeus[34] believed that high molecular weight colloids in plasma caused aggregation, and he introduced the concept of "suspension stability." Grönwall and Ingelman[50] demonstrated that high molecular weight dextran produced aggregation and decreased oxygen consumption, and that low molecular weight dextran reversed these changes. Thorsén and Hint[102] proposed that the existence of a film composed of a gel phase of macromolecules on the surface of erythrocytes caused their aggregation. Lee and Walsh[68] have produced data suggesting that "one rigid form of intravascular hemagglutination may result from the adsorption of altered globulin macromolecules onto the red blood cell membrane with a subsequent partial polymerization of these molecules to form intercellular bridges or to clump cells together in a gel-like mass."

Currently, low molecular weight dextran appears to alter erythrocyte sludging and to reduce blood viscosity by four basic mechanisms. The first mechanism is the rapid plasma volume expansion that results in fluid dilution and a reduction in hematocrit value.[45, 80, 106] With a decreased hematocrit value the blood viscosity is lessened. The plasma protein concentration also decreases with fluid dilution, with subsequent improvement in the fluidity of blood.[23] Secondly, low molecular weight dextran may form a complex with plasma fibrinogen, and hence temporarily abate the known effect on viscosity by fibrogen.[73, 79] The third mechanism of action to explain the influence of low molecular weight dextran upon the microcirculation involves the affinity of the dextran for the erythrocyte membrane, and subsequent alteration of erythrocyte changes. Bernstein,[14, 16] and Bernstein and Evans[15] have suggested that erythrocyte negativity is increased and the erythrocytes are repulsed. Finally, low molecular weight dextran exerts a siliconizing effect upon injured walls of blood vessels, resulting in peripheral flow improvement[17] (Table 1). Wells[105] has compared the effects of low molecular weight dextran on blood viscosity and the sludging phenomenon in vitro and in vivo, and has shown that in vivo low molecular weight dextran exerts a profound effect of lowering blood viscosity (the effect of infusions of saline under similar circumstances is negligible). He also observed that bulbar conjunctival blood flow was increased in patients with erythrocyte sludging during infusion of low molecular weight dextran. This study adds evidence to the concept that low molecular weight dextran possesses a distinct disaggregating effect upon erythrocyte sludging in addition to the hemodilution effect resulting from its oncotic properties.

Table 1. *Mechanisms of Action*

1. Plasma-volume expansion
2. Formation of dextran-fibrinogen complex
3. Alteration of erythrocyte surface charge
4. Siliconizing effect on injured walls of blood vessel

TOXICITY AND CONTRAINDICATIONS

Although severe toxicity results after infusion of high molecular weight dextran, no major toxic effects have been reported with the use of low molecular weight dextran. As a colloidal hypertonic solution, low molecular weight dextran will attract water from the extravascular space. If existence of congestive heart failure is suspected, or if the patient is poorly hydrated, low molecular weight dextran should be given with caution and in small amounts.

A possible hazard exists in the acidotic metabolites liberated into the general circulation upon improvement of peripheral blood flow after administration of low molecular weight dextran. A transient increase in acidosis may occur before there is excretion of the metabolites in the urine.[82]

The effect of low molecular weight dextran upon blood clotting is minimal. Clinical experience with its use in vascular surgery in a large number of patients revealed that bleeding tendencies did not develop.[37] The nature of the hemostatic defect or antithrombinogenic effect induced by the clinical use of dextran is obscure. Low molecular weight dextran in doses of from 1 to 1.5 gm. per kilogram of body weight did not change the bleeding time or platelet count in dogs.[84] In numerous investigations there has been no demonstration of a blood coagulation defect after low molecular weight dextran infusions in doses of 20 ml. or less per kilogram of body weight. When low molecular weight dextran is used as part of the priming solution for extracorporeal perfusion, slightly more than usual bleeding will occur. This is a reflection of the rheologic influence of low molecular weight dextran, which tends to decrease erythrocyte aggregation and to promote peripheral blood flow.[38]

In normal doses, low molecular weight dextran does not alter blood types or require changes in cross-matching.[74]

Cases of renal failure have been reported to occur after the use of low molecular weight dextran.[26, 48, 107] Although the preexisting clinical condition of those patients most likely accounted for their anemia, it is possible that low molecular weight dextran may have contributed to the failure.

The antigenicity of dextrans is directly related to their degree of branching. Since low molecular weight dextran has only a slight degree of branching, it is relatively free of antigenic effect. Allergic reactions principally manifested as mild urticaria have been observed in a few

Table 2. *Contraindications to Use of Low Molecular Weight Dextran*

1. Pulmonary edema
2. Congestive heart failure
3. Renal failure
4. Severe dehydration
5. Thrombocytopenia
6. Hypofibrinogenemia
7. Localized septic process

patients. In a few instances, nausea, chills, and fever have occurred. No anaphylaxis has been reported.

Contraindications to the use of low molecular weight dextran are pulmonary edema, congestive heart failure, renal failure with severe oliguria or anuria, hypofibrinogenemia, severe dehydration, and localized septic processes (Table 2).

DOSAGE AND ADMINISTRATION

Low molecular weight dextran is intended for intravenous administration only. It should not be given by any other route. It is available as a sterile, nonpyrogenic solution in 500 ml. infusion bottles as 10 per cent in normal saline, or 10 per cent in 5 per cent dextrose in water. It has a tendency to crystallize when subjected to temperature variations or when stored for long periods at elevated temperatures. It should be stored at room temperature, and if flakes of dextran appear they can be dissolved by heating for a short time at 100° C. or autoclaving at 110°C.

The usual effective adult dose is 500 ml. every 12 hours until improvement is noted. When used as the sole priming solution or an additive in the pump oxygenator, 10 to 20 ml. per kilogram of body weight is used. Total dosage should not exceed 1 gm. of dextran per kilogram of body weight. In children the total quantity and rate of administration must be reduced by one half.

CLINICAL USE AND EFFICACY

The use of low molecular weight dextran has been suggested for the treatment of many seemingly unrelated problems, such as hemorrhagic shock, cardiac bypass, burns, thrombosis, fat embolism, frostbite, myocardial infarction, crush injuries, pancreatitis, after vascular surgery, and in perfusion solutions. It has also been used for the treatment of cerebral ischemia, sickle-cell anemia, and bowel obstruction. The common denominator of these conditions is a low microcirculatory flow state with poor tissue oxygenation. Low molecular weight dextran is considered to be of therapeutic value because of its actions upon the microvasculature (Table 3).

Table 3. *Indications for Clinical Use of Low Molecular Weight Dextran*

1. Shock
2. Extracorporeal circulation
3. Peripheral vascular surgery
4. Acute ischemia of a limb
5. Fat embolism
6. Perfusion solution

SHOCK

In the last few decades much information has accumulated about the problems associated with surgical shock. Prevention and treatment of shock with the use of low molecular weight dextran was first advocated by Thorsén and Hint.[102] Gelin[39] investigated blood sludging in post-traumatic states, and is a strong proponent of the ability of low molecular weight dextran to prevent or to reverse ineffective microcirculatory flow because of cellular aggregation. Portal venous flow is significantly increased after administration of low molecular weight dextran in animals,[93] and striking improvements in cardiac output, hepatic blood flow, and renal blood flow have occurred after the use of low molecular weight dextran in humans.[23] Baker and associates[7] have reported remarkable responses in four patients with diminished compliance from primary pulmonary disease or prolonged cardiac bypass. They suggest the use of low molecular weight dextran to counteract the occurrence of massive sludging of erythrocytes during administration of multiple transfusions and mesentery venous thrombosis. Gruber, Bergentz, and Fritjofsson[52] believe that low molecular weight dextran should be used as the replacement solution of choice in the initial treatment of hypovolemia, because of the immediate large-volume increase which cannot be obtained with any other substance. From 500 to 1000 ml. of low molecular weight dextran can be infused for the treatment of hemorrhagic shock until properly cross-matched blood is available. Although volume expansion may account for much of the response, the rheologic effects of low molecular weight dextran on erythrocyte aggregation may play a role in decreasing regional vascular resistance. The use of low molecular weight dextran in situations involving hemorrhagic surgical shock appears to be indicated.

EXTRACORPOREAL CIRCULATION

Erythrocyte aggregation has been shown to accompany prolonged extracorporeal circulation and has been implicated as a cause of death.[16] Poor microcirculatory flow under these circumstances is thought to occur because of the denaturization of plasma protein which takes place in the interface between gas and blood in the bubble and disk oxygenators.[100] Low molecular weight dextran has been shown to possess certain advantages over blood and other solutions during cardiac bypass. It delays the onset of and decreases the sludging under these circumstances.[75] Low molecular weight dextran is being used either as the sole prime or as part of the priming volume in the pump oxygenators by many authorities. A statistically significant decrease in the destruction of erythrocytes and platelets has occurred as compared with blood alone, or with blood and albumin.[76] Direct observation of the conjunctival vasculature revealed that low molecular weight dextran prevented or lowered sludging during cardiac bypass. No adverse effect was noted upon bleeding, blood loss, clotting time, fibrinogen levels, and postopera-

tive blood loss through the chest tube. When low molecular weight dextran (10 per cent in 0.9 per cent saline) was given in amounts greater than 20 ml. per kilogram of body weight for priming a heart lung-machine with a rotating stainless steel disk oxygenator, there was a significant increase in the mean operative blood loss in one series of patients.[19] In a series of 72 patients undergoing cardiopulmonary bypass no significant effect on hemolysis was noted with the use of low molecular weight dextran as compared with the use of whole blood.[54] In another study, comparisons were made of low molecular weight dextran with 5 per cent dextrose, with 5 per cent dextrose and water, with low molecular weight dextran and blood in equal parts, and with low molecular weight dextran only.[77] Of the four solutions, low molecular weight dextran as the sole prime was the most effective in terms of lessened blood destruction. In comparison with whole blood, Martinovic and Melrose[78] also confirmed the lessened hemolysis and reduced platelet depression with low molecular weight dextran in 50 patients undergoing cardiopulmonary bypass.

Low molecular weight dextran is less expensive than large quantities of blood or albumin. It possesses the added advantage over blood in that there is a reduction in the danger of serum hepatitis or transfusion reaction.

The dosage of low molecular weight dextran employed in the priming fluid will vary with the volume of the pump oxygenator used. Generally, from 10 to 20 ml. per kilogram of body weight is added to the perfusion circuit. Total dosage should not exceed 2 gm. of dextran per kilogram of body weight.

Peripheral Vascular Surgery

Low molecular weight dextran is thought to exert an antithrombinogenic effect on operative trauma to small vessels.[108] A bleeding tendency that occurred when infusion was begun preoperatively was averted by giving low molecular weight dextran immediately after completion of the vascular suture. In 98 arteriolar reconstructions in 85 patients, 1000 ml. of low molecular weight dextran was given to each patient every 24 hours for five days. The hematocrit values decreased approximately 20 per cent during treatment with low molecular weight dextran. There was no wound hematoma and bleeding tendencies did not develop.[37] Bergentz, Eiken, and Gelin[12] also advocated the use of low molecular weight dextran postoperatively in patients who have undergone arterial reconstruction.

Acute Ischemic Limb

Low molecular weight dextran was observed to exert a beneficial effect by preventing gangrene and preserving limb function in acute ischemic limbs in dogs.[63] Bergan and associates[9] found that low molecular weight dextran provided dramatic relief of ischemic pain when given

to patients with acute ischemia. They recommended its use early after the onset of acute arterial occlusion, but believed that the use of low molecular weight dextran was not indicated for the chronic ischemic state. Folse and Cope[36] also concluded that the theoretic benefits of low molecular weight dextran did not prove to be of practical importance in improving the circulation of patients with arteriosclerosis obliterans.

Dramatic case reports cite the use of low molecular weight dextran in the treatment of vascular insufficiency after severe trauma.[87, 88] Low molecular weight dextran has also been suggested as useful to maintain patency of the microcirculation in the limb stump after amputation.[58]

Fat Embolism

Recent studies of the underlying pathophysiologic mechanism of the fat embolism syndrome have shown that an alteration of the normal plasma colloidal dispersion of chylomicrons occurs after trauma, and coalescence into larger fat droplets ensues.[31, 32] This factor, combined with the known changes that occur in post-traumatic microcirculatory flow, provides the physiologic basis for the fat embolism syndrome. Treatment is now directed at improving microcirculatory flow patterns by using low molecular weight dextran. Several authors have advocated its use in the treatment of this severe complication.[10, 13, 27, 33, 81] Five hundred milliliters of low molecular weight dextran is administered by intravenous infusion every 12 hours for the duration of symptoms.

Perfusion Solution

The use of low molecular weight dextran as a perfusate for extracorporeal circulation has been discussed. Low molecular weight dextran has also been successfully used for perfusion of organs, especially the kidney before transplantation.[29, 55-59]

Other Uses of Low Molecular Weight Dextran

In the last few years a wide variety of procedures and pathologic states have involved the use of low molecular weight dextran either clinically or experimentally. Beneficial results with low molecular weight dextran have been obtained through improving capillary circulation after frostbite.[83, 96]

Large clinical trials using low molecular weight dextran in myocardial infarction are now under investigation.[64-66, 72] The preliminary results seem to indicate that the immediate mortality can be improved, but carefully controlled long-term studies are not yet available.

Infusion of low molecular weight dextran may improve the acute phase of necrosis of the anterior segment of the eye.[85]

Low molecular weight dextran has also provided increased protection in experimental strangulation obstruction of the bowel, and has been advocated for use in humans.[1]

The freedom from the risk of a hemorrhagic complication is an obvious advantage over anticoagulation in the treatment of cerebral ischemic episodes.[67] Low molecular weight dextran is also thought to prevent brain damage during profound hypothermia and circulatory arrest.[30]

Levy, Trippel, and Bergan[71] reported the successful use of low molecular weight dextran in phlegmasia cerulea dolens. It has also been used in the treatment of purpura fulminans.[86]

The influence of low molecular weight dextran on vascular and intravascular responses to contrast medium has not been impressive.[25]

Studies with dogs revealed that low molecular weight dextran may intensify rather than reduce the fluid losses that occur with the increased vascular permeability of acute experimental pancreatitis.[2] A double-bind trial with the use of low molecular weight dextran in the treatment of bone pain crises in sickle-cell disease revealed that low molecular weight dextran was no more effective than 5 per cent dextrose in water alone.

Bioelectrically induced thromboses did not respond to the administration of low molecular weight dextran but responded to the administration of heparin, plasma, and clinical dextran.[35] Other experimental studies in regard to dextran specificity in thrombus inhibition revealed that clinical dextran (molecular weight 75,000) was more effective than low molecular weight dextran in preventing thromboses.[90] The same phenomenon was found to exist in the treatment of thrombophlebitis both experimentally and clinically.[20]

Several other conditions in which blood flow within the microvasculature may be compromised have been suggested as amenable to treatment with low molecular weight dextran.[92] Currently there is not enough evidence to warrant its use in these problems.

SUMMARY

Studies of the development of the dextrans as colloidal solutions, and subsequently the emergence of low molecular weight dextran as an effective agent to reverse or inhibit erythrocyte sludging are presented. The pharmacology, mechanisms of action, toxicity and contraindications, and clinical uses of low molecular weight dextran are discussed.

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Hyperbaric Oxygen

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In recent years physicians representing diverse medical disciplines have evaluated experimental and clinical responses to hyperbaric oxygen. Clinical interest in this therapeutic modality arises from the importance of hypoxia in determining an unfavorable clinical course for many diseases. Furthermore, conventional oxygen therapy at normal atmospheric pressures commonly proves ineffective in ameliorating illness complicated by hypoxia. Recent investigations during hyperbaric exposures have delineated the quantitative increase in oxygen delivery to tissues as well as useful biologic responses. Severe manifestations of toxicity from hyperbaric oxygen also occur; these hazardous and potentially irreversible reactions limit the tolerated dosage to brief multiple exposures of less than 3 atmospheres absolute (ATA). Careful evaluation of clinical experience indicates that there are few well accepted therapeutic indications at this time. Opportunities for wider usage await both development of effective measures for preventing toxicity and improved techniques of gas delivery to ischemic tissues.

RATIONALE FOR HYPERBARIC OXYGEN

Normal environmental air has sufficient weight to support a column of mercury 760 mm. high against a vacuum. This so-called "quicksilver" measure of pressure or tension can be expressed also as 1 atmosphere absolute (ATA). Regardless of the source, inspired gas equilibrates rapidly in the body tissues to a total tension approximating environmental pressure. Increasing the total gas or oxygen tension in blood and tissues beyond 1 ATA requires exposure of the recipient to an increase in environmental pressure in a hyperbaric chamber.

Oxygen comprises 20.938 per cent of environmental air and exerts a tension equal to the product of this concentration and atmospheric pressure (760 mm. Hg $\times$ 0.20938 = 159 mm. Hg). This simple computation of partial pressure reflects not only the quantities involved but the principle (Dalton's law) that each gas exerts tension and acts independ-

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ently of other gases in a mixture. This normal partial pressure (Po_2) of oxygen in air provides an adequate concentration gradient to insure delivery of sufficient substrate to meet metabolic requirements in normal man despite widely varying conditions in tissues of oxygen consumption, structure, function and perfusion.

Conduction of inspired air across the alveolar capillary structures of the lung into arterial blood causes a fall of Po_2 because of dilution and consumption. The resultant 100 mm. Hg tension permits the physical solution of only 0.3 vol.% of this insoluble gas in the aqueous compartment of blood.[31] This amount obviously cannot meet intracellular needs, since 1 liter of blood would transport only 3 ml. of dissolved oxygen. However, blood contains a unique pigment, hemoglobin, which combines chemically with oxygen at this partial pressure; therefore, a liter of blood containing 150 gm. of hemoglobin will transport chemically 201 ml. of oxygen.[27] Fortunately, the characteristics of oxyhemoglobin dissociation are such that oxygen combines readily at tensions normally present in the pulmonary capillaries and dissociates readily in the peripheral tissue capillary bed at the prevailing lower Po_2's of less than 70 mm. Hg, thereby becoming available for metabolic use.

Computation and indirect measurements indicate also that despite adequate perfusion the Po_2 normally may fall below 3 mm. Hg in diffusing across the extravascular space to the mitochondrial site of consumption within the cell.[19] This remarkable decrease of Po_2 while traversing a distance computed to be less than 0.1 mm. indicates that there are profound limitations of extravascular diffusion for this insoluble gas. As a result oxygen therapy becomes ineffective in many forms of tissue hypoxia due to ischemia; the associated increase of effective intercapillary distance prevents improved oxygenation of affected cells despite hyperoxygenation of the environment, lungs and arterial blood.

If pure oxygen is breathed instead of air, the inspired Po_2 increases almost five-fold. Assuming that hemoglobin in arterial blood was already fully oxygenated, the resultant increase in transport is only 1.5 vol.% when the Po_2 increases from 100 to 600 mm. Hg because of limited physical solubility ($600 - 100 \times$ the oxygen solubility factor 0.003). The physical solution of oxygen in blood conforms closely to Henry's law for slightly soluble gases, and increases linearly as the Po_2 rises; therefore, a very large increase in Po_2 would increase oxygen transport by blood substantially. For example, at a Po_2 of 2000 mm. Hg the volume of physically dissolved oxygen would exceed 6 vol.%. Tensions of this magnitude can be obtained only at increased environmental pressures, and this relationship provides the major rationale for therapeutic use of hyperbaric oxygen (Table 1).

There are two apparent theoretical advantages to be derived from hyperbaric oxygen at the tissue level. First, the absolute number of oxygen molecules delivered in each unit of blood should increase. Second, the higher Po_2 should increase the extravascular penetration of oxygen and enlarge the volume of tissue protected from hypoxia by diffusion from a single capillary.[6] Where perfusion of a tissue is normal or moder-

Table 1. *Theoretical Relationships Between Respiratory Gas and Arterial Blood for Oxygen Tension and Content**

ATMOSPHERIC PRESSURE (atm. abs.)	BREATHING GAS	INSPIRED AIR P_{O_2}	ALVEOLAR GAS P_{O_2} (mm. Hg)	ARTERIAL BLOOD P_{O_2} (mm. Hg)	ARTERIAL BLOOD O_2 CONTENT (vol.%)
1.0	Air	149	110	110	20.4
1.0	O_2	760	673	673	22.2
3.0	O_2	2280	2193	2193	26.9

*The water vapor gas tension (47 mm. Hg) and carbon dioxide tension (40 mm. Hg) have been subtracted from atmospheric pressure in order to calculate the alveolar P_{O_2}. Perfect pulmonary gas exchange has been assumed as has the absence of venous admixture. In practice these and other factors less clearly identified will cause a substantial decrement, with the resultant P_{O_2} in arterial blood being less than that of alveolar gas.

ately reduced, substantial improvement in oxygen delivery may occur during hyperbaric exposure. Where perfusion is very low and the extraction of oxygen is very great, or where blood flow to a tissue is virtually absent, one might anticipate little improvement of oxygenation at the cellular level despite very high tensions in arterial blood.

In a given setting of oxygen consumption, homogenous distribution of capillaries and reduced perfusion, hyperbaric therapy may restore normal oxygenation of a tissue. For practical benefit, however, the therapist must assume that abundant quantities of other essential metabolic substrates reach the cell despite ischemia. This assumption is supported to some extent by experimental evidence, suggesting that oxygen is the most flow-limited of the nutrient materials required for tissue metabolism.[16]

PHYSIOLOGY AND PHARMACOLOGY OF HYPERBARIC OXYGEN

Because of increased gas density, the effort of breathing rises at higher atmospheric pressures and there is more resistance to flow through the tracheobronchial tubes.[22] This increased effort is not excessive for a normal individual breathing quietly but becomes appreciable with hyperventilation or if the airway lumen is reduced artificially with a tracheostomy tube. Theoretically, the greater fraction of turbulent intrapulmonary air flow in patients with chronic pulmonary disease would be an additional factor increasing the effort of hyperbaric respiration.

Lung compliance, vital capacity, lung volumes and the rate of transfer for carbon monoxide across the lung-blood barrier remain unchanged during hyperbaric exposures or during brief exposures to hyperbaric oxygen.[29] Furthermore, the increase of P_{O_2} in arterial blood reflects linearly the increase of P_{O_2} in inspired gas at hyperbaric pressures, although the measured P_{O_2} of arterial blood may be 10 or 15 per cent lower than the computed alveolar value.[29] The contribution of inequalities of ventilation and perfusion, inboard leading of environmental

Table 2. *Mean Blood Oxygen Responses to Hyperbaric Oxygenation in 10 Normal Subjects*

ATMOSPHERIC PRESSURE (atm. abs.)	INSPIRED GAS	ARTERIAL BLOOD Po_2 (mm. Hg)	ARTERIAL BLOOD O_2 (vol.%)	VENOUS BLOOD CONTENT Po_2 (mm. Hg)	VENOUS BLOOD CONTENT O_2 (vol.%)
1	Air	89 ± 3.2*	19.1 ± 0.32	41 ± 0.9	14.9 ± 0.47
1	100% O_2	507 ± 13.9	21.2 ± 0.51	57 ± 3.5	17.2 ± 0.51
3.04	100% O_2	1721 ± 33.5	25.2 ± 0.51	424 ± 77.8	20.7 ± 0.54

*One standard error.

nitrogen into the alveolar compartment, and measurement error in producing these gradients is not clear (Table 2). Nevertheless, the increased volume of oxygen in free solution alone in arterial blood at a Po_2 approaching 2000 mm. Hg will meet overall metabolic requirements of the body, and hemoglobin remains fully saturated with oxygen in venous blood returning to the heart.

During hyperoxygenation the cardiac output and heart rate decrease, calculated peripheral vascular resistance increases, stroke volume remains relatively constant, and changes in mean blood pressure are small and variable.[34] As the blood oxygen tension rises higher, systemic blood flow falls to a yet lower volume. As might be anticipated, regional blood flow, as measured in muscle, limbs, brain and kidney, also falls.[17] Alterations of regional blood flow are similar but not identical to changes observed for cardiac output.

Direct observation reveals vasoconstriction when the Po_2 rises in arterial blood.[28] In normal man these changes have been quantitated thoroughly in the retinal blood vessels. Here the decrease in vessel diameter is roughly proportional to the rise in oxygen tension and is independent of barometric pressure or hypocapnea.[1]

At hyperbaric oxygen pressures beyond 2½ ATA venous hemoglobin remains bright red, despite obvious vasoconstriction and a known decrease of regional blood flow, indicating a higher concentration of oxyhemoglobin and a greater net availability of oxygen for metabolic requirements.

Because many therapeutic applications of hyperoxygenation depend upon enhanced tissue oxygen storage, considerable effort has been expended to determine the ability of tissues to retain increased amounts of oxygen and to utilize this increased supply efficiently. Computations based on known physical and chemical characteristics suggest that increases in body oxygen stores are meager during exposure to hyperbaric oxygen. Adequate methods for measuring intracellular tension directly are lacking and most investigators have relied on techniques demonstrating that after exposure to hyperbaric oxygen normal function of an organ will persist longer when perfusion is interrupted. With total circulatory arrest, as in electrically induced ventricular fibrillation, prolongation of viability or retained organ function is comparatively brief. If the circulatory arrest is prolonged beyond 10 minutes, the hyper-

oxygenated experimental animal is difficult to resuscitate.[23] The use of hypothermia, vasodilators (such as inhaled carbon dioxide), or incomplete interruption of blood flow may extend greatly the time interval during which the animal can be retrieved.

In man, this phenomenon can be tested easily by measuring the duration of retained vision during temporary retinal ischemia.[9] The experimenter induces ischemia by applying pressure upon the eyeball. Vision will persist for only a few seconds at ambient pressure but after exposure to 4 atmospheres of oxygen the subject may continue to see a test object with his ischemic eye for as long as a minute. Although limited increases of oxygen storage can be demonstrated functionally, total ischemia leads invariably to loss of function after a comparatively short time, and irreversible tissue damage occurs unless adequate blood flow is restored promptly. Therefore, these experiments emphasize further the major role of perfusion in determining the adequacy of any technique for augmenting oxygen delivery to a tissue.

OXYGEN TOXICITY

Hyperbaric oxygen in excessive doses is toxic and can cause serious damage or death. The forms of oxygen toxicity most easily identified in man are of two types: central nervous system and pulmonary.[4, 32] The central nervous system form is characterized by pallor, nausea, nervousness, a sense of suffocation, restlessness and finally a major seizure or syncope. The victim recovers promptly when removed from the hyperoxic environment. If the oxygen exposure continues, however, the unconsciousness will terminate in death. Susceptibility to this form of oxygen toxicity varies remarkably, not only in different species but within the same animal group. Oxygen pressures in excess of 4 ATA cause symptoms of central nervous system toxicity in man within a few minutes. This form of toxicity can be avoided, however, by limiting the hyperoxic exposure to less than 2½ ATA. Pulmonary oxygen toxicity of a progressive and irreversible type develops upon prolonged exposure to one or more atmospheres of oxygen pressure. Extensive clinical experience suggests that gross pulmonary oxygen toxicity can be avoided in patients if uninterrupted exposures to hyperbaric oxygen are limited to 5 hours or less. Many workers regard even these brief exposures as being tolerated rather than being free of harmful effects.

The obvious implication of these practical constraints is that the patient with brief requirements for improved oxygenation is more likely to benefit than the patient with hypoxia due to chronic ischemia.

The underlying subcellular biochemical changes associated with oxygen toxicity are complex. Changes include irreversible impairment of cellular respiration, depletion of enzymes, lowered concentrations of high energy phosphates, and in red blood cells the occurrence of lipid peroxidation.[10, 13, 20, 30] A variety of antidotes has been tested, including such antioxidants as alpha tocopherol (vitamin E), altered endocrine activity, hypothermia, hypocapnea and administration of intermediate

compounds, such as succinate, to sustain intracellular metabolic activity. To date no pharmacologic agent has been proved to protect man and the problem remains as serious as when first described more than a century ago by Paul Bert.[4]

SIDE EFFECTS OF HYPERBARIC PRESSURES

Untoward responses to increased atmospheric pressures include dysbaric effects on gas-containing body cavities, inert gas narcosis and decompression sickness or air embolism. During compression, respired gases enter the body tissues and gas-containing cavities and seek equilibrium with the environment. If equilibrium is not attained, the resulting negative pressure causes severe pain in cavities such as the sinuses and inner ear. Ruptured tympanic membranes and bleeding from sinuses are not rare. These problems are rare when hyperbaric oxygen therapy is administered by experienced personnel, and they do not inhibit hyperbaric exposures in the absence of upper respiratory infection. When the patient is unconscious, however, myringotomy should be performed prior to the therapeutic exposure.

During exposure to increased atmospheric pressure, personnel accompanying the patient ordinarily breathe air containing 80 per cent nitrogen. At hyperbaric pressures in excess of 4 ATA nitrogen produces a narcotic sensation which Costeau has termed "the rapture of the deep."[12] The psychological effect is similar to alcoholic intoxication in that the subject performs familiar procedures with relative efficiency compared to his lack of success in learning new tasks. This phenomenon of inert gas narcosis correlates closely with the physical characteristics of the molecule; the heavier molecule of nitrogen is a far more potent cause of narcosis than helium or hydrogen. The recognition of nitrogen narcosis in air-breathing personnel is of major concern to hyperbaric therapists, since skilled coordinated efforts such as cardiovascular surgery could be impeded at greatly increased atmospheric pressures.

The inert gases absorbed by tissues during hyperbaric exposure must leave the body through the pulmonary "window" during decompression in order to maintain equilibrium with the environment. If decompression occurs too rapidly, stored gases may be released in the form of bubbles; the resultant diffuse clinical syndrome is termed decompression illness or the "bends."[2] Like nitrogen narcosis, this problem applies primarily to attending personnel, since they breathe air during the hyperbaric exposure and accumulate increased amounts of inert gas in their tissues. Because patients breathe pure oxygen, their tissues lose nitrogen continuously during a hyperbaric exposure, and clinically recognized symptoms of decompression sickness will not occur from increased absorption of oxygen. The clinical picture of decompression sickness may include central nervous system involvement with paralysis, coma and death. Milder, more common manifestations include pruritus, joint pain, abdominal pain and transient visual aberration (Table 3).

Table 3. *Aspects of Decompression Sickness*

Mild symptoms and signs
Pruritus, formication, rashes
Fatigue
Transient visual disturbance
Localized pair or bends
Serious manifestations
Unconsciousness
Convulsions
Weakness or paralysis
Visual disturbance
Dizziness
Loss of speech or hearing
Severe shortness of breath or "chokes"
Shock
Sequelae
Aseptic bone necrosis—particularly at ends of long bones, i.e., knee or elbow; rarely occurs among closely supervised divers who follow standard decompression procedures
Permanent neurologic deficit—generally a result of delayed or inadequate treatment of acute central nervous system involvement

To prevent decompression sickness, air-breathing personnel must decompress gradually so that tissue gases can escape without bubble formation. Staged decompression schedules devised empirically by the United States Navy are in common use for this purpose. Shorter oxygen decompression schedules have been developed, based upon the principle that oxygen breathing widens the gradient between tissues and alveolar gas for nitrogen, thereby accelerating washout of this inert gas. The margin of safety for these tables would be reduced by significant ingasing of nitrogen through a poorly fitting face mask, however.

Despite theoretical calculations and much empiric experience, decompression schedules in the biomedical pressure ranges are inadequate. The problem is complicated further because members of a medical health team vary greatly in physical characteristics and may be more vulnerable to the hazards of decompression sickness than carefully selected divers. Experience with decompression sickness in medical hyperbaric chambers has varied with the depth of exposure and the decompression schedules employed. No significant episodes of decompression sickness have occurred during the past two years in the Duke facility (using a modified United States Navy air decompression schedule). Modifications of the Navy Schedule include conservative interpretation of tables, slow decompression between interval stops, particularly during the final ascent, and the breathing of pure oxygen during the final 15 minutes. Despite all of these precautions the hyperbaric therapist should be prepared to meet effectively the rare occurrence of decompression sickness. Furthermore, similar therapeutic requirements are generated by serious air embolism in the cranial circulation as a result of gas entering blood in an aberrant manner during passage through the lungs or during cardiotomy. The practical implications of this responsibility are considerable and are reviewed in a subsequent section.

FIRE IN A HYPERBARIC CHAMBER

In the confined space of a hyperbaric chamber, fire can spread rapidly and engulf exposed personnel. Increased atmospheric pressures and higher oxygen concentrations accelerate the rate of burning. Because of decompression requirements and mechanical limitations no rapid escape is possible. For this reason elaborate precautions to prevent ignition and preparation to meet the consequences of failure are essential. Modern medical hyperbaric facilities incorporate numerous ingenious preventive and fire-quenching techniques. Their value is not greater, however, than the skill and alertness of responsible personnel.

CLINICAL RESPONSE TO HYPERBARIC OXYGEN AND HYPERBARIC AIR

Currently there are three generally accepted categories of illness for which the hyperbaric therapist can offer optimal therapy: (1) decompression sickness and air embolism; (2) carbon monoxide poisoning; and (3) gas gangrene caused by the Clostridium welchii organism. There is, in addition, much promise in the dramatically successful experience of one group with palliative surgery of severely cyanotic infants suffering from congenital heart disease. Also, combined hyperbaric oxygen and irradiation therapy seems to have special merit in the treatment of certain inoperable tumors. Promising observations in tissue storage and transplantation, skin grafting, chronic osteomyelitis, vascular insufficiency, coronary heart disease and acute cerebral ischemia merit comment as well.

Increased atmospheric pressures will reduce the volume of gas bubbles caused by *decompression sickness* or *air embolism*, or will return them into solution. One well established regimen requires compression to 6 ATA with gradual decompression over a 12 to 39 hour period for treatment of "bends" or an aeroembolic episode causing a major neurologic deficit. More recently developed successful regimens combine hyperbaric pressures of lesser magnitude and pure oxygen breathing. The denitrogenation caused by oxygen breathing lowers the tension of inert gas in tissues, thus accelerating diffusion of nitrogen from gas bubbles. Either of these regimens will lead to dramatic, prompt improvement in a majority of selected patients with symptoms of recent onset.[14, 26]

The efficacy of hyperbaric oxygen in preventing hypoxic damage from *carbon monoxide poisoning* has been recognized for many years. Recent quantitative studies in man and clinical experience in patients indicate multiple benefits from prompt exposure for 1 hour to 2½ atmospheres of oxygen pressure. Sufficient oxygen can be forced into physical solution in blood to maintain viability of hypoxic tissues despite the absence of sufficient functioning oxyhemoglobin. Also, increasing the oxygen tension in blood to 2½ ATA will accelerate the washout of carbon monoxide from the body and will restore the concentration of

oxyhemoglobin in blood to a normal level during the exposure. Finally, the inhibiting effect of carboxyhemoglobin in preventing release of oxygen from available oxyhemoglobin is minimized by the hyperbaric exposure.

In 1960, Boerema and Brummelkamp reported remarkable improvement in patients suffering from *gas gangrene due to Clostridium welchii* after seven 2-hour exposures to hyperbaric oxygen at 3 ATA over a 3-day interval.[5] Subsequent experience from many hyperbaric centers has been favorable. A comparatively low mortality rate, prompt defervescence, and early loss of toxicity early in the sequence have been consistently observed. In practice, the response to hyperbaric oxygen has been sufficiently good that surgeons have deferred necessary debridement to a time of election. Rationale for this remarkable experience rests upon the intolerance of anaerobic organisms to oxygen. Yet, the very circumstances which allow successful implantation of this organism in man, notably severe tissue trauma with resultant hypoxia and ischemia, limit the effective penetration of hyperbaric oxygen to the interface between viable, perfused and nonviable, nonperfused tissue. Inactivation of toxins produced by this organism may contribute to the clinical response.

A physiologic explanation has been offered as well. At hyperbaric oxygen pressures the small bubbles of gas produced by this organism are reduced in size and are theoretically cleared more rapidly, thereby reducing the embolic ischemic effect of free gas in tissues. These physiologic events should be associated with improved perfusion and better delivery of oxygen to involved tissues. Some support for the latter explanation may be inferred from the fact that clinical experience has not been impressive with other forms of anaerobic infection exposed to hyperbaric oxygen.

Gray demonstrated that improved oxygenation would restore the radiosensitivity of *hypoxic tumor cells* which were otherwise resistant to irradiation.[15] In a rapidly growing tumor some cells lack an adequate blood supply and become hypoxic. Hypoxic tumor cells might account for failure to sterilize certain malignancies with irradiation. For this reason Churchill-Davidson tested combined hyperbaric oxygen and radiotherapy in a lengthy series of patients suffering from inoperable tumors.[11] His experience and subsequent observations indicate clearly that combined therapy will increase tumor sterilization, decrease morbidity and prolong survival. An occasional patient will become free of detectable tumor and remain so (Table 4). Of the malignancies evaluated to date, nasopharyngeal tumors have responded best. Because these patients with tumors are not acutely ill in most instances and do not require continuous nursing, radiotherapists have found that the economical, one-man, plastic or aluminum hyperbaric chamber is practical. Despite encouraging experience, combined radiotherapy and hyperbaric treatments for malignancy has not yet won general acceptance. Most patients with inoperable tumors die within a relatively short time and these therapeutic regimens yield only modest improvement.

Within the past three years, Bernhard and colleagues at the Boston

Table 4. *Results in Patients with Advanced Tumors Treated with Combined Hyperbaric Oxygen and Irradiation*

	SURVIVAL TIME AFTER TREATMENT				
	1 YEAR	3 YEARS	5 YEARS	7 YEARS	9 YEARS
Total number of patients	178	130	89	58	20
Number of patients without recurrence	72	17	8	7	2
Per cent without recurrence	40	13	9	12	10

Children's Hospital have performed palliative surgery employing hyperbaric oxygen in more than 100 small infants deteriorating rapidly from severe *congenital cyanotic heart disease* (Table 5).[3] Survival and improvement has followed in most of these children. Bernhard et al. have enjoyed success as well with the use of hyperbaric oxygen in conjunction with surgery for *acyanotic* heart disease in infants. In addition to obtaining a vastly improved survival in comparison to their earlier experience, this group has observed that bradycardia and hypotension commonly developing during surgery at ambient pressure will resolve promptly when the infant is exposed to hyperbaric oxygen. In congenital cyanotic heart disease, the Po_2 of arterial blood is often very low (under 30 mm. Hg), with resultant severe desaturation of hemoglobin. Even during exposure to hyperbaric oxygen, a large right-to-left extrapulmonary shunt allows only a modest increase of the Po_2 in aortic blood. Nevertheless, a small increase of Po_2 in this low range will improve oxygen transport remarkably, because a much larger fraction of hemoglobin in aortic blood becomes oxygenated. Additional experience in other centers, incorporating control series, will help evaluate the contribution of hyperbaric oxygen in improving management of comparable patients.

Table 5. *Hyperbaric Surgery for Congenital Heart Disease*

DIAGNOSIS	NO. OF PATIENTS	ALIVE	% LIVING
Palliative			
Transposition of great vessels	33	27	82
Tetralogy of Fallot	18	15	83
Pulmonary atresia, with intact I.V. septum	10	7	70
Tricuspid atresia	8	4	50
Ventricular septal defect and pulmonary Arterial hypertension (pulmonary artery hypertension)	10	10	100
Atrioventricularis communis (pulmonary artery hypertension)	5	4	80
	84	67	80
Corrective			
Aortic stenosis	7	5	71
Pulmonic stenosis	11	11	100
Coarctation of aorta (pulmonary artery hypertension)	4	2	50
	22	18	82

The occasional patient with *acute cerebral ischemia* of less than 7 hours' duration will improve dramatically, with prompt resolution of a major neurologic deficit, when exposed to hyperbaric oxygen.[18] Perhaps one of three such patients responds in this manner, with improvement persisting in 50 per cent. The relationship of hyperbaric oxygen to improvement could be appreciated most clearly in two patients obtaining only temporary benefit. In both instances hemiplegia and coma cleared completely within a few minutes of exposure to hyperbaric oxygen. The improvement persisted for an hour after termination of the hyperbaric exposure, with subsequent relapse followed by temporary restoration of normal neurologic function when the patients were again exposed to hyperbaric oxygen. Experiences of this type indicate the persistence of viability in areas of the central nervous system which lack neural function shortly after the ischemic attack. This form of treatment may have greater value, however, if hyperoxygenation is combined with methods for restoring patency of the involved cerebral blood vessel.

Ischemic skin grafts may survive more often if the patient is exposed frequently to 2 atmospheres of oxygen pressure.[24] The encouraging series reported to date have been conducted in a one-man type of chamber in which hyperbaric oxygen gains access to the flap by respiratory and topical pathways. Observers report prompt conversion of a cyanotic color in skin flaps to a bright red hue, as well as restoration of normal capillary filling. Because experience with skin grafting varies widely at individual institutions, these observations should be regarded as preliminary until further experience is gained.

Refractory chronic osteomyelitis with draining lesions, unresponsive to combined medical and surgical regimens for as long as 10 years, has been reported consistently to heal when accepted regimens are combined with daily brief exposures to 2 atmospheres of oxygen pressure.[25] Although hypoxia may contribute to defective healing, this rationale has not been tested critically and additional observations are needed to evaluate these preliminary reports.

There is great interest in the therapeutic application of hyperbaric oxygen for *acute myocardial infarction.* Improvement over present results would be of great value in this common serious illness of modern man. The problem has proved extremely difficult to evaluate, however, since the incidence of death is low for a single attack and an adequate series of high risk patients has not been reported to date. In one controlled series of 40 patients no significant difference in mortality was observed when the hyperoxygenated group was compared to controls.[7] Subsequent observations from the same center have indicated some favorable hemodynamic responses associated with hyperbaric oxygen, and occasional case reports have described dramatic improvement of a deteriorating patient.[8, 29] There are some indications from both experimental and clinical observations that the major benefit would come from improved control of serious arrhythmias. From a practical therapeutic standpoint, however, excellent alternative means for treating most arrhythmias already exist that are simpler to execute. Therefore, hyperbaric therapists need techniques for selecting appropriate patients

who are unlikely to respond when treated with conventional medical regimens.

Workers in *organ transplantation* have demonstrated that hyperbaric oxygen at 3 to 6 ATA, hypothermia and pharmacologic agents can maintain viability of stored kidneys in a nonperfused setting for up to 72 hours.[21] This increase in the interval of useful storage simplifies the logistic task of mating transplant to recipient.

Patients with chronic *ischemia of the lower extremities* have improved transiently when exposed to hyperbaric oxygen. Favorable responses do not persist, however, and the probability of major benefit in chronic peripheral vascular insufficiency seems small with the present constraints of intermittent short therapeutic exposures.[29] When an acute process supervenes, however, and in particular when the vascular insufficiency may be due to a reversible process such as vasculitis, intermittent exposure to hyperbaric oxygen may conserve limbs and save life. In one reported instance of purpura gangrenosa in a 19 month old youngster with severe involvement of the legs, ears and fingers, intermittent exposure over a 5-day period to two atmospheres of oxygen reversed the cyanotic changes, decreased pain and led ultimately to complete recovery.[33]

SUMMARY

This review has described the rationale for hyperbaric oxygen and the known biomedical responses. The serious and unsolved hazard of oxygen toxicity limits practical tolerated exposures to less than 3 atmospheres of oxygen pressure for uninterrupted periods of no more than 5 hours. As a result, therapy with hyperbaric oxygen at the present time seems most practical for clinical problems where brief, multiple exposures can offer a reasonable opportunity for clinical improvement. Major therapeutic successes have been observed for hyperbaric oxygen in the management of decompression sickness and air embolism, carbon monoxide poisoning and gas gangrene. Furthermore, patients with certain inoperable tumors respond better to radiotherapy when it is combined with this new therapeutic modality. An impressive good experience has been reported in palliative surgical management of congenital cyanotic heart disease in infants. Also, patients suffering from acute cerebral ischemia, ischemic skin grafts and refractory chronic osteomyelitis have improved remarkably in some instances after treatment. The ultimate contribution of hyperbaric oxygen to the broad field of vascular surgery and in the management of coronary heart disease has not been evaluated adequately up to the present time. In the future, wider clinical application will require the physician to prevent the emergence of oxygen toxicity in patients so that the limits of this therapeutic modality can be explored adequately.

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ADDITIONAL ARTICLE

Back Braces: Types, Functions and How to Order and Use Them

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There is no logical reason why the general practitioner cannot learn to prescribe back braces just as well as the orthopedic surgeon. He will have no trouble doing so, if he learns the contents of the following pages.

GENERAL INFORMATION ABOUT BACK BRACES

The correct type of back brace is one of the most valuable adjuncts in the treatment of acute and chronic back pain of musculoskeletal origin. When properly used a brace will lessen the amount of pain, speed the rate of recovery, and make recovery more complete. This is because a painful back becomes more painful with movement; a brace stops that movement and therefore lessens the pain when it is correctly used.

If the proper type of back brace for the patient's spine is used, it very likely will be of great benefit, but if the wrong type is used it will do no good and it may do harm.

It is exceedingly important, therefore, that you know what type of back brace to use for the different types of pathological conditions that involve the spine.

For example, suppose the patient has an injured 5th lumbar disc and stands in a position of low back flexion; that is, he leans forward and cannot straighten up very well, and when he tries to he has pain. A hyperextension back brace will cause the patient to have more pain and it may actually lead to additional backward protrusion of the disc; thus the brace will be of no value and it might be harmful.

Suppose you order a chairback or a flexion type of back brace for a patient with an anterior compression fracture of almost any vertebra in the thoracic or lumbar spine. If you do and the patient wears it, the brace will not do any good and it may do harm because it will permit additional compression of the fractured vertebra.

In medical schools and in postgraduate courses there has never been any concerted effort made to inform the general practitioner of the

different types of back braces, their functions, how to use them, and the indications for the use of each type. In this paper I shall attempt to do so.

There are nine different types of back braces. Each performs a different function and each is used for a certain, definite, specific purpose. The types are: (1) chairback back brace; (2) flexion type back brace; (3) hyperextension type back brace; (4) scoliosis type back brace; (5) conditioned reflex–lumbar posture brace; (6) conditioned reflex scoliosis harness; (7) celluloid or plastic brace; (8) sacro-iliac belt; and (9) lumbosacral corset supports.

FUNCTIONS PERFORMED BY BACK BRACES

Back braces can be built to perform the following functions:

1. A brace may immobilize and support all or part of the spine in a normal, neutral, erect, straight position.

2. A brace may hold the back in a position of hyperextension—a leaning backward or swayback position.

3. A brace may hold the spine, particularly the lumbar spine, in a position of flexion.

4. A back brace may support the scoliotic spine and attempt to prevent further settling of the curve.

5. A back brace may be built in such a way as to hold the patient in a leaning sideways position. This type of brace is used sometimes in the treatment of scoliosis.

6. A web strap type of brace may be built to induce corrective conditioned reflex and conditioned response reactions for early scoliosis.

7. A brace may be built to induce a conditioned reflex and conditioned response reaction, which will develop tone and strength in weak abdominal muscles, plus improving the patient's posture.

8. A sacro-iliac belt will lessen mobility and thus pain in diseased sacro-iliac joints.

A back brace will not do any good in the following conditions: (1) primary or metastatic malignancies involving the vertebral column; (2) intraspinal tumors of any kind; (3) referred pain from prostate, kidney, or abdominal and pelvic organs; and (4) a large backwardly protruding intervertebral disc making pressure on a nerve root *with sciatic pain.*

Back braces will be of benefit in the following conditions: (1) certain fractures of the spine; (2) muscular and ligamentous strains and sprains; (3) degeneration and settling of intervertebral disc; (4) injury of any one or more intervertebral discs when there is no associated nerve root pressure; (5) painful hypertrophic arthritic change in the spine; (6) rheumatoid arthritis involving spine articulations (Marie-Strümpell arthritis); and (7) sacro-iliac arthritis. In addition, a brace may be used instead of a cast to limit motion in the spine following a surgical fusion operation.

Musculoskeletal abnormalities that will be benefited by a brace usually have the following three things in common: (1) localized muscle

spasm in the area where the back is painful; (2) a limited range of movement in a certain part of the back, usually the area where the pain is located; (3) pain occurs or if already present is aggravated by these movements of the spine.

There is no constant muscle spasm when the back pain is caused by disease of the prostate, kidneys, or abdominal or pelvic organs. Seldom is there muscle spasm with intraspinal tumors. There may, however, be muscle spasm with primary or metastatic malignancies involving the vertebral column if there is bone destruction; hence movement of the back would be painful and the range of motion would be limited by the tight spasm of the muscles surrounding the lesion.

For the most part, however, the presence of these three things—muscle spasm, limited motion in the back, and pain that is produced or aggravated by motion—indicates that the back trouble can be benefited by a back brace. A thin patient will almost invariably get relief from pain more quickly and more completely with the use of a back brace than the fat patient, because in the fat patient there is so much soft compressible flesh between the metal of the brace and the bone of the skeleton that when the patient moves, the soft flesh moves and compresses, thus allowing a good bit of motion to occur within the confines of the brace. If the patient is too fat, have him lose some weight. This is necessary if he expects to get a good result from the back brace.

CHAIRBACK BACK BRACE

Figure 1 shows a chairback type of back brace (Knight type). Its function is to *immobilize the lumbar spine in a neutral, straight*

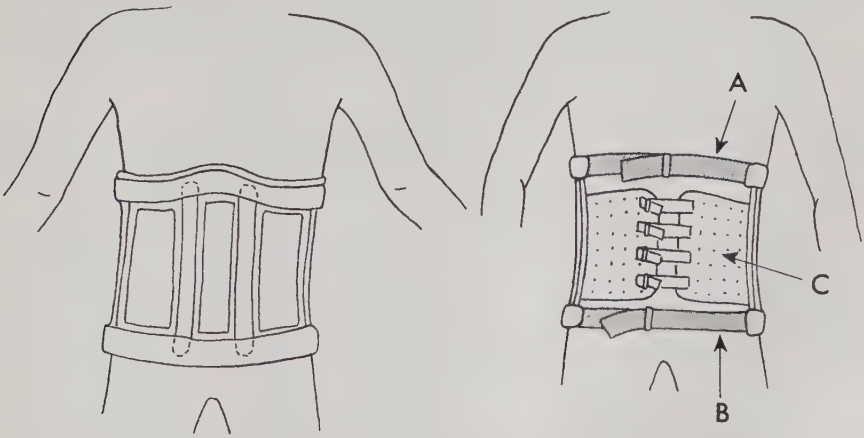

Figure 1. This is probably the best type of back brace ever designed for immobilizing the lower spine in a straight natural position. Many chairback braces do not have the separate upper and lower front web straps, here designated by *A* and *B*. These straps are very important additions to the chairback brace and should be on all of them.

The apron or "front," *C*, usually is made of rubber, perforated for coolness. If a patient leans forward against the rubber apron it stretches enough to permit some spine flexion to occur. Strap *A* is not elastic; thus it does limit flexion to a marked degree. Strap *B* holds the brace more securely on the pelvis than an apron alone does.

position. There are several other braces designed for this same purpose, which are a little different in construction or shape from this one. All of them work reasonably well, but the chairback back brace, with separate upper and lower front web straps, is probably the best of all of them, because it is mechanically more efficient than almost any other type of back brace designed for this specific purpose.

Indications for a Chairback Back Brace

Assume that it has already been determined from the history and the examination that the back pain is not referred from some internal organ, and is not caused by a neurological disorder such as intraspinal disease or tumor.

Most, but not all, of these patients with low back pain give a history of an injury. The patient says that movement—stooping, bending, twisting, exertion, any movement—aggravates the pain in his back and that rest relieves it, sometimes completely, sometimes only partially. Some patients find that lying down on a hard surface makes the back feel better. Most find that lying down, getting the weight off the back, makes it feel better regardless of whether it it a hard surface or not. To examine the patient, have him standing naturally and as relaxed as possible with his back to you; he should be disrobed from the greater trochanter area upward. First, feel of the muscles of his back and see if they are soft and yielding to the pressure of your finger tip, as is normal, or if they are hard and rigid in constant spasm. If there is localized muscle spasm, then in all probability the pain is due to some abnormality in the bones, joints, ligaments, muscles, or discs in that area of the spine. Muscle spasm is nature's way of immobilizing the spine, preventing motion in it that would be painful; hence a brace that helps the spasmodic muscles immobilize the painful area will be helpful.

Palpate for tender spinous processes. Usually the third, fourth, or fifth lumbar process will be tender.

Ask the patient to bend to the left and to the right to see whether motion is free or limited and to find out if he complains of pain. If there is pain with left or right bending, a chairback back brace will stop these movements, and relieve the pain.

Then ask the patient to lean backward as far as he can; if there is pain, (there usually is), a back brace will limit this movement and thus lessen pain.

Ask the patient to bend forward. *If he has pain on bending forward,* then more than likely he will need a chairback type of back brace, because this brace is designed to limit motion in all directions.

Notice whether the back is pulled off sideways by muscle spasm, what we call a side list of the spine. If the patient does list to the left or right and all these other things are true—that is, pain occurs with forward, backward, and left and right bending—then the chairback brace is indicated, but it should not be worn while the patient has the list. The list usually will disappear after a week's rest in bed, with enough sedation to keep the patient comfortable, perhaps muscle-relaxing medication, and application of heat to the back. It usually takes about a

week to have the brace built. Do not attempt to apply a straight chairback back brace to a patient with a side list, because it will not fit and it will be uncomfortable.

A chairback back brace limits backward and forward bending to a marked degree and left and right bending to an even greater degree. Inasmuch as these movements cause pain and the back brace stops them, it will relieve the pain. The brace is simply assisting the normal, natural physiological processes of repair. The spasmodic muscles are trying to hold the back still and immobile. The brace does the same thing, but it does it mechanically, giving the spasmodic muscles a chance to rest, so that muscle soreness subsides while the back is still being held rigidly immobile with the brace. The brace assists nature in its reparative processes.

The indication for a chairback type of back brace is musculoskeletal pain in the lumbar region *which is aggravated by movement in all directions.* The brace will stop most of the movement and thus be of benefit.

After the brace has been applied to the patient, he should be examined with it on to be sure that it is built right, is high enough and fits well. The patient should be told that he must not expect too much relief the first week that he wears the brace, but after the first week, after he has become accustomed to it, then the brace will give much more benefit.

I always give the patient a mimeographed set of instructions concerning the wearing of the back brace. I ask him to read these instructions two or three times until he learns what the brace does and how it does it, so that he will be able to take full advantage of the supporting and immobilizing effect of the brace.

Instructions to the Patient on the Wearing of the Chairback Back Brace

Always wear the brace over a cotton undershirt which will absorb sweat.

It usually takes about a week or ten days to become thoroughly accustomed to the brace. You have never worn anything like this before, with metal strips running up and down the back and on either side of your back; hence it will take you at least a week to become accustomed to the feel of it. During the first week that you are wearing it, you will not notice as much relief as you will the second week. The reason is that during this first week you will be squirming and wiggling around inside the brace at frequent intervals, trying to get your back accustomed to the feel of it. You will be moving your back more than you would otherwise. After one week, though, when you have become accustomed to the brace, relief will be much more rapid and much more complete. *You will get some relief the first week, but much more in the second week.* From the second week on you should notice a steady, progressive improvement.

You should return to my office at the end of one week after the brace is applied because there are usually one or two places on the brace that are too tight or too loose and need adjusting. You will not be able to feel them the first day but after you have worn the brace a week we can tell what final adjustments should be made to be sure it is worn properly, in the proper place, that it is adjusted properly, and that it does exactly what it should do.

During this coming week, while you are getting accustomed to the brace, learning how to put it on, take it off, and wear it, you are to spend the *major part of your time lying around resting.* I suggest that you lie down for one hour in bed

every morning, in the middle of the morning, and again for one hour in the middle of the afternoon. When you lie down for as long as an hour, you may take the brace off and then put it on again when you get up. However, two or three other times during the day you should lie down for 10 or 15 minutes at a time. When you lie down no longer than 10 or 15 minutes you may leave the brace on.

How the Brace Helps You

The brace helps you by supporting your back, and by immobilizing it.

By supporting the back, I mean that it provides the feeling you have when you are tired and you slump down, and you feel your back pressing against the two upright bars of the back brace, which give you a feeling of support in the back. When something touches your back, just simply presses against it lightly, it creates a feeling of support or stability and this feels good to the patient with a sore back.

The ability or capacity of a brace to immobilize the back does two things for you. First, it lessens pain. The lower back, where the damaged 4th or 5th lumbar vertebra is, hurts with movement. The brace stops movement. You have heard the doctor say you have muscle spasm in your back, and you can probably feel the rigid, tense, tight spasm of the muscles in the lower part of your back. That is nature's method of bracing or splinting the spine. The natural reparative processes of nature are trying to hold your back still, because if the back is held still, healing will occur at a much more rapid and much more complete rate in the damaged area. A brace, therefore, assists nature; it assists those natural reparative processes of your body by mechanically holding the spine still, so that healing can occur more quickly and more completely.

There is also a long term result that accrues from immobilization. The 4th of 5th lumbar vertebra that is causing the pain is abnormally movable. It is so unstable that with almost any movement you make that bone moves unduly and this causes pain. If the vertebra that is too loose is tightened, that should relieve your pain. One way of doing this is by a bone graft operation on your spine, but there is another way. Let me explain it as follows:

Suppose you have a cast on your arm for three months. When the cast is removed, your elbow will be stiff. That is exactly what we want to happen to your vertebra. It is too loose, and we want to stiffen it up. We could apply a cast to your back but for practical purposes, we don't use a cast, which is heavy and uncomfortable. You can't remove it to take a bath, and it doesn't fit and hold as well as a brace does, because the tightness of a brace can be adjusted from time to time as needed. A brace holds the spine immobile and allows the loose vertebra to tighten up, and when it tightens up, with fibrous tissue formation all around it, and becomes more stable, your pain will be gone and it is not likely to recur unless another strain or injury stretches and tears the fibrous tissue thickening that has grown around the vertebra.

Getting Into and Out of Bed

Now that you know how the brace helps you by *supporting* and by *immobilizing* your back, you can realize that you either have to wear the brace night and day, or, if you take it off at night, you must be careful not to let the back bend; if you let the back bend in going to bed and in getting up, you will defeat the purpose of the brace and your recovery will not be so swift and so complete.

When you go to bed, therefore, take all your clothes off except the brace, sit on the edge of the bed, slip the brace off, lean forward carefully, bending at the hip joints and not in the spine, and carefully set the brace on a table or a chair by the side of the bed. Then lie down sideways in the bed, carefully put your feet on the bed, and then turn over on your back. If you do this, you hold your back straight and still and rigid, and you do not defeat the purpose of the brace.

To get up, turn over on your side, draw up your knees and hips, and then push yourself up sideways, holding your back rigid and straight as you do this. *Do not*

let the back bend. This then places you in a sitting position with your feet off the edge of the bed. Before you do anything else put the brace on. After you have put the brace on, then go ahead with your other activities and put on the rest of your clothes. Do this every time you get in and out of bed.

In the Bathroom

You will bend your back when you get in and out of the bathtub, if you bathe in the ordinary way. Therefore, when you use the bathtub, carefully remove the brace, carefully sit down on the edge of the tub, holding the back rigid, and carefully take a sponge bath. Hold the back still. Do not let it bend while you are taking the bath. *Better still, take a shower bath.* Hold the back still until you get the brace on again.

In sitting down on the commode, either leave the brace on or, if the brace is off, make a distinct effort to hold the back straight and prevent motion in it.

When you sit down your brace may tend to slide upward an inch or so. This is particularly true in women, who have a broader pelvis than men. When you stand, if your brace has slid upward, put your hands on the sidebars of the brace and push it downward, back into its proper position before you start walking.

Some people wear the brace night and day, but we don't recommend it. It usually is too uncomfortable to wear at night. By observing the precautions described here and not letting the back bend at night or while in the bathroom, you can get the same permanent beneficial effect as if you wore the brace all day long and all night too.

This set of instructions is of great value, because sometimes a patient becomes discouraged during the first three or four days he is wearing the brace, unless he has read these instructions and understands what the brace does and how it does it.

The back brace usually is worn for three months. The doctor should decide when to remove it. When the patient tells you his back feels good and he has no pain with movement and no muscle spasm remains, then the brace is no longer needed.

HYPEREXTENSION BACK BRACE

There are two general types of hyperextension back braces. The one that has been used the longest is called the Taylor type of back brace, and is shown in Figure 2, *A*. Within the last few years another hyperextension back brace has become popular, called the Jewett type (Fig. 2, *B*). The Jewett back brace is mechanically more efficient than the Taylor type, but either one will serve the purpose for which the brace is designed, that is, to hold the spine in hyperextension, if it is properly applied and properly worn. There is another "anterior hyperextension" type of brace (Lennox Baker) that maintains hyperextension by three point pressure, like the Jewett brace, and it, too, is satisfactory.

Indications for a Hyperextension Back Brace

Sometimes a hyperextension brace is used on growing children who are developing a postural roundback, but that is not the main or most satisfactory use.

The most important and most common use of the hyperextension back brace is for *anterior compression fractures* involving the verte-

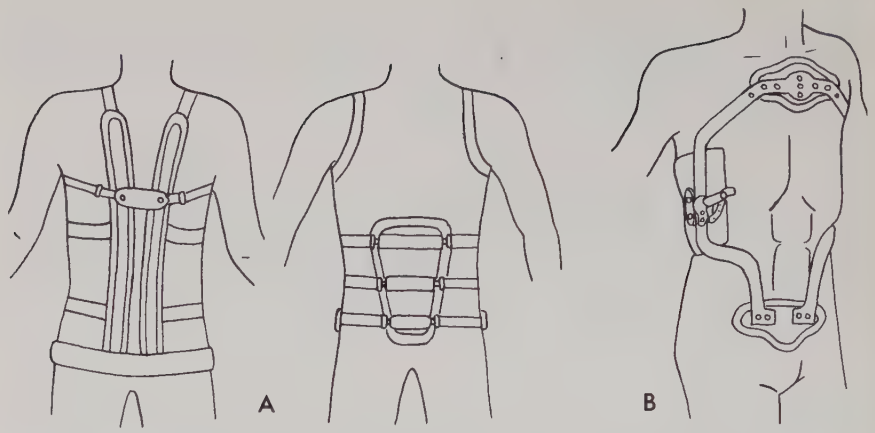

Figure 2. *A*, Back and front views of a Taylor type hyperextension back brace. *B*, Jewett hyperextension back brace.

brae in the midportion of the spine, usually the 11th and 12th thoracic or 1st and 2nd lumbar. Figure 3 shows the effect hyperextension has on these fractures. Care should be exercised in prescribing a hyperextension back brace for a patient with a fracture involving the posterior portion of the vertebral body, adjacent to the spinal cord (Fig. 3, *C*). If you are not an expert with these fractures, have a specialist see the patient because this kind of fracture may require recumbency and traction or even surgery instead of a brace.

Most patients with slowly progressive rheumatoid arthritis of the spine (Marie-Strümpell arthritis) will get a great deal of benefit from wearing the hyperextension brace, because it immobilizes the spine, thus diminishing pain, and it prevents the patient from developing a fixed, flexed roundback deformity, as often occurs.

In exceedingly rare instances a patient with an injury of the lower lumbar spine (not a fracture) will feel better with a hyperextension brace. The way to determine whether a hyperextension back brace will help in a low back injury is to find out if the patient feels better when he is standing with his back in extension, a swayback posture. The patient stands in front of you with his back exposed. Ask him to lean to the left and to the right. If these side movements are painful, immobilization of the back would be beneficial because a brace will stop them. Then ask him to bend forward. When he does he will keep the back in extension (a swayback position) and bend forward at the hips or bend the knees. He will not let his lumbar spine flex, but maintains the swayback posture, and he probably will complain of pain. Then ask the patient to lean backward. If he says that it feels better, then a hyperextension back brace is indicated for a low back injury. This is an extremely rare occurrence.

The two main reasons for the use of hyperextension back braces are: A compression fracture, with anterior compression only, of the vertebral bodies (this usually occurs about the 11th or 12th thoracic or 1st

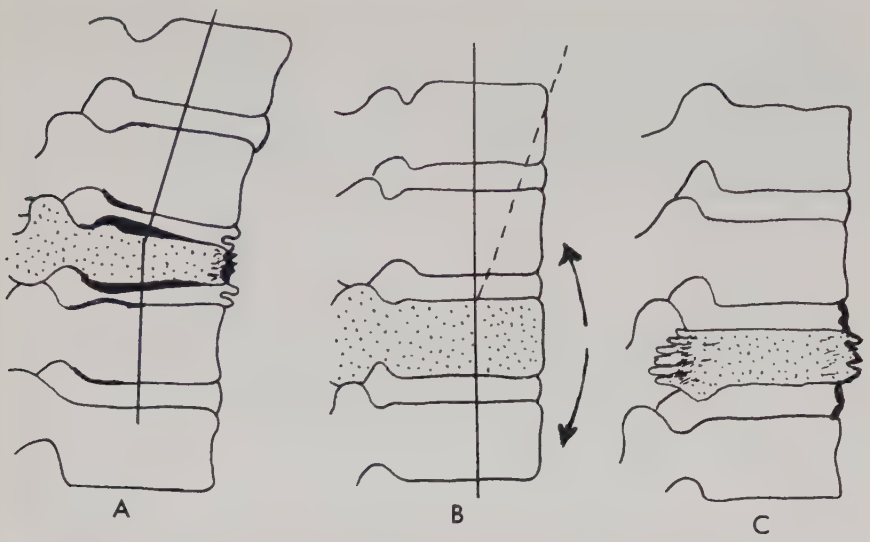

Figure 3. *A*, Note anterior compression of one vertebral body (the one stippled). This is the most common fracture that occurs in the spine. Note that the anterior longitudinal ligaments, which are normally taut between all of the normal vertebral bodies, are wrinkled or folded and loose on the compressed one. Usually the anterior longitudinal ligament is not torn at the time the compression fracture occurs.

B, The spine in extension. The anterior longitudinal ligaments pull the flattened vertebral body back to its normal position when the spine is extended.

C, The stippled vertebral body here shows how a vertebral body is sometimes compressed posteriorly as well as anteriorly; thus part of the posterior portion of the body of the vetebra bulges backward into the spinal canal. This is the type of fracture in which the spine must not be hyperextended, because that position may increase the pressure on the spinal cord and might cause paralysis.

and 2nd lumbar area); and progressive chronic spinal arthritis (Marie-Strümpell type), for which a good hyperextension back brace properly worn will prevent the patient's bending more and more forward until he finally becomes an arc with his face looking at the ground.

INSTRUCTIONS TO THE PATIENT ON THE USE OF THE HYPEREXTENSION BACK BRACE

Always wear the brace over a cotton T-shirt which will absorb sweat. Your brace cannot be comfortable the first week or ten days that you wear it. You are not accustomed to wearing a couple of rigid metal bars running up your back or, if you are wearing the Jewett type, to having pressure in the middle of the back and over your pubic bone and sternum. If you are using the Taylor type of back brace, the straps that go around the shoulder will irritate you at first, but you can take care of the early temporary irritation by placing some felt padding or some strips of cotton mattress padding at the place where the straps are irritating the skin. In time the skin will become sufficiently toughened that you can keep the straps tight and thus maintain your back in hyperextension without any undue irritation under the armpit or in front of the shoulder. You must keep the shoulder straps snug and tight. If you don't you might as well not have the brace on.

Most braces of the Jewett type are locked in place, so that they cannot slip and you cannot lose correction. You wear the brace night and day. It doesn't take long to become accustomed to it.

Of course you don't like the feel of the brace, but you don't like a fractured vertebra either, or spinal arthritis, and of course, the child doesn't like the brace, but the child doesn't want to grow up with a roundback deformity. With a little time and patience you will become accustomed to the restraining forces of the brace and you may even, after a while, find them comfortable.

Patients with anterior compression fractures usually need brace support for three to four months. If the brace is worn to prevent flexion deformity in spinal arthritis, it will have to be worn for a much longer period of time.

FLEXION TYPE OF BACK BRACE

Figure 4, *A*, shows a Williams flexion type of back brace. There are no vertical upright bars in the middle of the back (as in the chairback brace), which, if present, would prevent full flexion of the spine. Note the side bars hinged at the top, with straps attached to the lower ends. These bars are designed so that, when the lower web strap in front is tightened, the bars exert pressure on the back in two places, behind the pelvis at the lower transverse bar and across the upper part of the lower back at the upper transverse bar, and a corresponding counterpressure over the abdomen in front. As you tighten the belt, the levers push forward on the upper bar, thus pushing the low back into flexion, which is the purpose of this brace.

Indications for a Flexion Type of Back Brace

The patient complains of low back pain, and he says that it is due to an injury. Usually his back feels better when he is sitting than when he is standing. Lying on the stomach may hurt more than lying any other way, and lying on the back with the knees bent feels better than lying on the back with the knees straight. Sometimes the patient will tell you that his back feels better when he stands in a leaning forward position.

Have the patient disrobe and stand with his back to you. He stands with his back in lumbar flexion and cannot straighten up—when he tries, it hurts. There is intense muscle spasm in the lower part of his back, so much that he does not have the normal lumbar lordosis. The low back is completely flat. This lordosis is completely obliterated by the position of lumbar flexion that this spasm induces.

There may be tenderness over some of the spinous processes of the lower lumbar spine, especially the fourth and fifth lumbar.

Leaning to the left and to the right is painful. The patient cannot lean backward very far and when he does it hurts severely. He can lean forward fully 45 degrees or more without much pain, and he will tell you that it feels better when he has leaned forward 20 to 25 degrees.

Have the patient lie down on his back on a firm table, and have him stretch his knees out straight. If this makes his back hurt, then bend both his knees and both hips up so that the bottoms of his feet rest flat on the table. He will usually say that this feels better.

Patients who respond this way to these various movement tests usually have an injured fourth or fifth lumbar disc. As the injured disc settles down and narrows the disc space, the bony walls of the nerve root

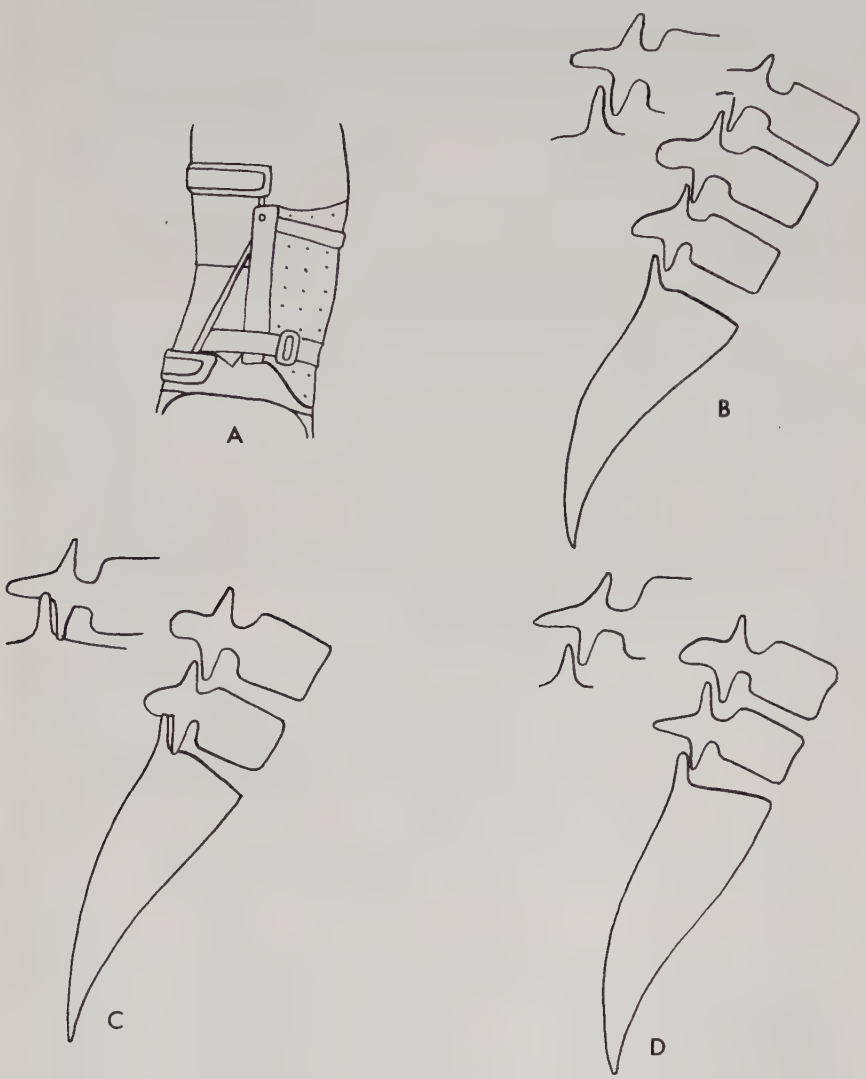

Figure 4. *A*, Flexion type of back brace.

B, Diagrammatic representation of the normal side view position of the sacrum and the 5th lumbar, 4th lumbar and 3rd lumbar vertebrae, with disk spaces and facet relationships normal (inset).

C, Diagrammatic side view of the sacrum and the 4th and 5th lumbar vertebrae, with the 5th lumbar disk narrowed. Note that the nerve root opening between the 5th lumbar and the sacrum is considerably narrowed as compared to the nerve root opening between the 4th and 5th lumbar. Note in the inset how the upper facet slides down on the lower one. This facet override places an abnormal stretch and strain on the joint capsule.

D, Diagrammatic side view of sacrum and 4th and 5th lumbar vertebrae, showing the 5th lumbar flexed on the sacrum. Even though the disk space is narrowed this position of flexion widens the nerve root opening behind, thus restoring the joints to a more nearly normal position (inset) and enlarging the nerve root opening.

opening become smaller (Fig. 4,*C*) and come closer into contact with the nerve root that emerges sideways from between the 5th lumbar disc and sacrum or between the 4th and 5th lumbar discs. When the patient leans backward, that nerve root opening becomes further narrowed. When he leans forward the nerve root opening is widened (Fig. 4,*D*); this is why he stands with a flat fixed lumbar spine and has pain if he leans backward.

When an intervertebral disc has been narrowed, the intervertebral joints or facets slide downward too far on each other (Fig. 4,*C*, inset). They override, and the chronic strain and stretch on each joint capsule produces chronic pain; increased pain on movement is due to the subluxated position of these facets.

If the lumbar spine is pulled forward into flexion, the facet surfaces are pulled back into a nearly normal position, so that when the joint capsules heal, they heal in a normal position, instead of in an abnormal, weak, unstable, subluxated position (Fig. 4,*D* inset).

A flexion brace limits left and right bending, prevents backward bending or hyperextension of the spine, and forces and holds the lumbar spine in a desirable position of flexion.

A patient with a *low back disc injury who has pain on bending forward* is helped by *a chairback type of back brace.* A patient with *low back disc injury whose pain is relieved by bending forward a little bit,* is helped by *the flexion brace.*

In the patient with a lower lumbar disc injury, when disc is protruding backward and exerting pressure on a nerve root, giving the patient *sciatic pain,* very likely neither the chairback nor the flexion brace will be of much benefit. When there are definite neurological findings of nerve root pressure on a nerve root, surgical removal of the protruding disc is usually indicated.

INSTRUCTIONS TO THE PATIENT ON THE USE OF THE FLEXION BACK BRACE

Always wear your brace over a cotton undershirt which will absorb sweat.

Your brace is designed for one main purpose – to force your lumbar spine into a flexed position and hold it that way. The lower part of your back must be held in a position as if you were purposefully bending forward about 35 degrees. When you do this, you widen the nerve opening through which the nerve emerges from the spine in order to eliminate pressure or irritation of the nerve and thus lessen your back pain. This position also places the joints between the sacrum and the 5th lumbar disc in a more normal position.

Because it is a dynamic brace, a brace that exerts a constant corrective force, it takes time to become accustomed to it. It is not like putting on a glove. A glove fits and is comfortable immediately if you have the right size, but a glove exerts no corrective force on the hand. New shoes of the correct size feel a bit different, but not uncomfortable, but you have already worn shoes all of your life, and you accept them without any difficulty at all.

Don't be discouraged, therefore, if it takes as long as a week to become accustomed to the feel of the brace.

This brace is not likely to slide upward when you sit down, but if it does, put your hands on the side bars of the brace and push it down to its proper position when you stand.

This brace stops motion in bending to the left and to the right and since those motions cause pain, it eliminates some pain that way. Bending backward causes a great deal of pain and since this brace won't let you bend backward, it relieves pain. Bending forward causes the nerve root opening in the back to widen; the brace forces your back into that position, releasing some of the pressure and irritation on the nerve. Bend with the brace, don't fight it.

With a little time and patience you will become so accustomed to it that it will be comfortable and later on, after two or three months of wearing it, you very likely will be reluctant to remove it.

SCOLIOSIS BRACES

There are many different types of scoliosis braces, but I will mention them here only briefly because scoliosis is a difficult problem, one for the orthopedic surgeon. Furthermore, each patient poses an individual problem. There is no one standard scoliosis brace that is consistently successful in all patients.

The most nearly successful brace for the growing child is the Milwaukee brace which fits around the pelvis, the body, the chin, and the occiput. It is a complicated brace and many brace makers cannot make it correctly. In addition, it needs daily or weekly adjustments by the orthopedic surgeon and the brace maker.

In an old lady, however, who has had mild scoliosis all of her life, but whose bones have become weak because of an insufficient calcium and protein intake, so that her curve is beginning to settle, thus producing pain, a back brace like the one shown in Figure 5, *A*, would be of some value, because it may prevent additional settling of the curve. It will support her back and give her a great deal of comfort.

Side Bending Scoliosis Brace

This brace holds the patient's upper spine, that is, from the 12th thoracic area upward, leaning to one side, and most often there is a projection upward from the brace that makes the head and neck lean to the same side (Fig. 5,*C*).

Indications for the Side Bending Scoliosis Brace

This brace is used in patients with scoliosis high up in the thoracic spine and lower cervical spine. Most of the curves that occur there are rather formidable ones. They are usually due to congenital wedge-shaped or trapezoidal-shaped vertebrae, or there may be one half of a vertebra growing on one side of the spine and none at all on the opposite side at the same level, so that the spine grows in a curve; the malformation is high enough in the spine that it involves the neck.

These patients are difficult to treat and should be referred to an orthopedic surgeon.

CONDITIONED RESPONSE BRACES

Although the use of bracing and splints is as old as the history of man, it was only about ten years ago that the first specific attempt was

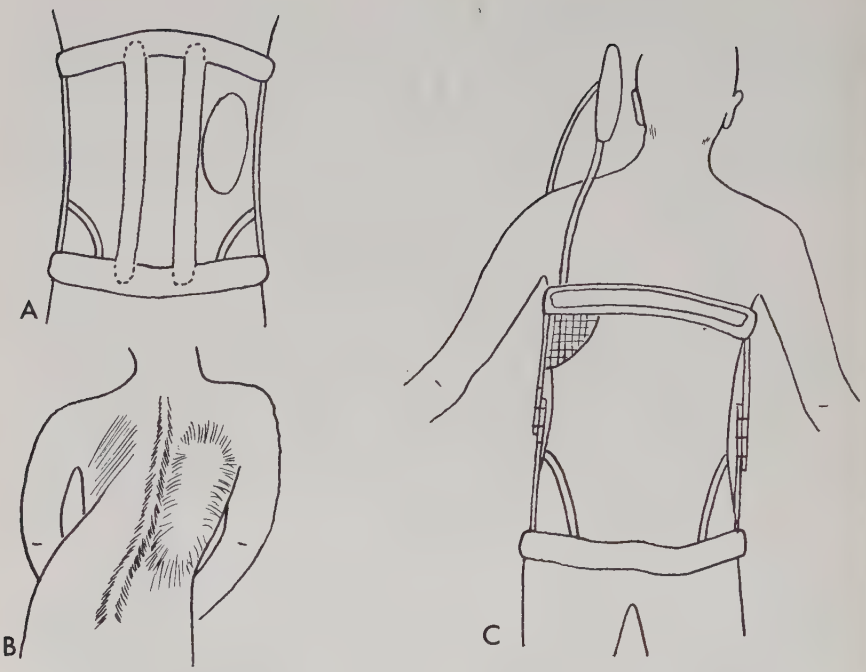

Figure 5. *A,* What might be considered an ordinary type of scoliosis brace. There is really no standard brace for scoliosis. Each brace has to be built individually for each individual patient, but this shows an ordinary Knight type of back brace with an oval pressure pad placed over the hump. Sometimes this is a fixed pressure pad; Sometimes it is a piece of leather covered with felt and attached to the bars on the opposite side of the chest with straps, so that you may have a variable degree of pull on that protruding part of the thorax.

B, Curvature of the spine with a hump on the back. This hump is the angular backward projection of the ribs, due to rotation of the vertebrae in the curve, which in this patient's case is on the right upper thorax. The pressure pad of the brace always presses against the hump.

C, This side bending type of brace is a very valuable one but is seldom used, because it is for those very rare high thoracic curves which extend up into the base of the neck, thus necessitating the upright piece against the side of the head to keep the head and neck pulled over the same way as the brace pulls the spine. The side bars are adjustable; they can be lengthened or shortened.

made to use the conditioned reflex or response as an adjunt to bracing.

Since then the conditioned response principle has been used in leg, foot, or arch braces, wrist braces, spine posture braces, and scoliosis braces.

However, because it is a relatively new idea, some of the older brace makers may not be familiar with the terms, nor do they know how to assemble the reflex producing device, a little sharp tack that touches the body and induces a muscular reflex.

If your brace maker is not completely familiar with the conditioned response principle, you may have to show him a picture of the brace with the little tacks in it in the appropriate places. Once he sees the picture, he will have no trouble making the brace for you.

SCOLIOSIS CONDITIONED REFLEX HARNESS

If you diagnose an incipient or very early flexible scoliosis in a child, idiopathic in type, then you would be fully justified in going ahead with the treatment, rather than sending the child to an orthopedic surgeon, because the treatment procedure is very simple and the results obtained in these early minimal flexible curves are exceedingly good.

Diagnosis of Incipient and Early Idiopathic Scoliosis

Seldom will the mother or the relatives of the child suggest to you that the child may be developing a curvature because he has no symptoms from his spine and the physical findings are minimal in degree. The condition must be sought by the physician.

Look at the child standing in front of you, disrobed from the greater trochanter level upward. If one loin consistently sinks in more than the other, or if there is a tilt of the shoulder girdle, or if both these abnormalities are present, then you may have found a beginning curvature of the spine (Fig. 6,*A*).

Observe the child two or three different times, front and back, *standing naturally.* If he always stands with this configuration of his body, then have an x-ray made.

This x-ray must be made *with the child standing* with weight equally distributed on both feet, with both knees straight and no elevation under either foot, and showing from the iliac crests upward (Fig. 6,*B*). *He must stand naturally.* If he stands rigidly straight like a

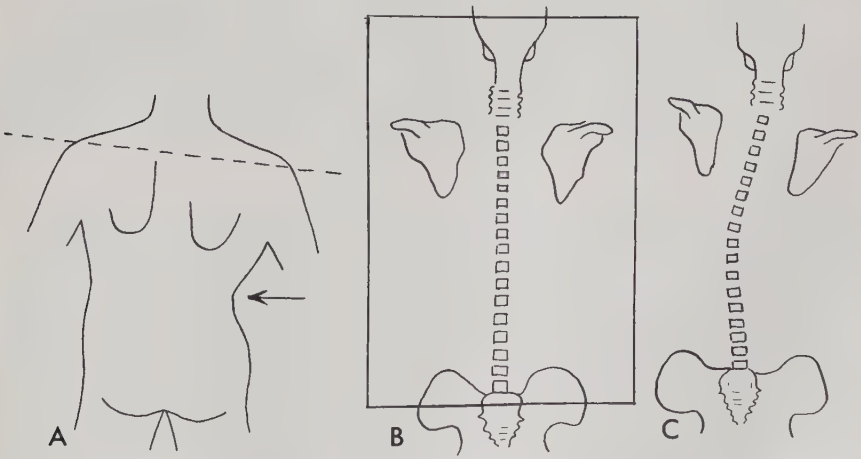

Figure 6. *A*, If one loin (flank) sinks in more than the other and this is consistently present every time the child stands, the child very likely has incipient scoliosis. It becomes even more likely if the shoulder girdle also is tilted.

B, How to position the 14- × 17-inch x-ray film in making a standing x-ray. Show only about an inch of the upper portion of the iliac crest and upward. Almost all of the rest of the spine will show on the film.

C, A diagrammatic representation of the type of C curve usually found in a very early or incipient scoliosis.

soldier, the curve will not show, because the flexible curve will be obliterated by his torso muscle action. An x-ray taken with the patient lying down probably will show a perfectly straight spine, but with him standing the x-ray will show a very slight curve. It is not a compound curve, like an S, but a C curve; it is so slight as to be hardly noticeable and usually the apex of the curve will be at the level of the 12th thoracic or 1st lumbar area (Fig. 6,*C*). Actually it is more of a side slump than a curve.

If you find such a curve, tell the mother that the child may be developing a spinal curvature, but that you cannot be sure, and have her bring the child back in a month. A month later, x-ray the spine again. Once more have the child *standing naturally*, weight equal on both feet, knees straight, with no elevation. If again you find the same type and degree of spine angulation or curve, no matter how mild it is, then it is still more likely that you have found a curve.

Read these films yourself. A roentgenologist probably will not appreciate the significance of these early minimal findings because he does not know what you are looking for.

However, it is still possible that the child just happened to be standing in that particular way when both pictures were made; have him come in again in a couple of months. Then if, for the third time, the spine shows the same type of slight curve in exactly the same way, you have found an incipient or early scoliosis, which untreated will mildly, slowly, painlessly progress until the age of puberty, when it very likely will progress rapidly and become a severe curve with considerable deformity.

Treatment of Incipient and Early Scoliosis

If the child does not have a congenital deformity, such as wedge-shaped or trapezoidal-shaped vertebra in his spine, and he has not had polio and thus muscle weakness on one side of his body, but he does have the findings just described and *the spine is flexible*, then by all means go ahead and treat him because the treatment is easy and the results are excellent.

Apply the scoliosis conditioned reflex harness to the child. This harness can be made by any person with a sewing machine. The side strap that has the tack in it *always should be placed on the convex side of the child's curve* (Fig. 7). Be very certain that it is on the convex side.

This brace does two things: (1) It makes the child constantly lean toward the side strap, thus withdrawing that side of his body away from the tack, so the tack will not stick him. When he leans that way, he is straightening or overcorrecting his curve. (2) It causes the child to develop the habit of standing (when he stands still) with all his weight on the leg on the convex side of the curve and with his opposite knee bent (Fig. 8), thus tilting the pelvis up on the convex side and down on the concave side. When he stands this way, the side strap is loosened and the tack does not stick him; the tilt of the pelvis induces a corrective force on the spine curve (Fig. 8).

In applying the scoliosis harness, be sure that the side strap is on the

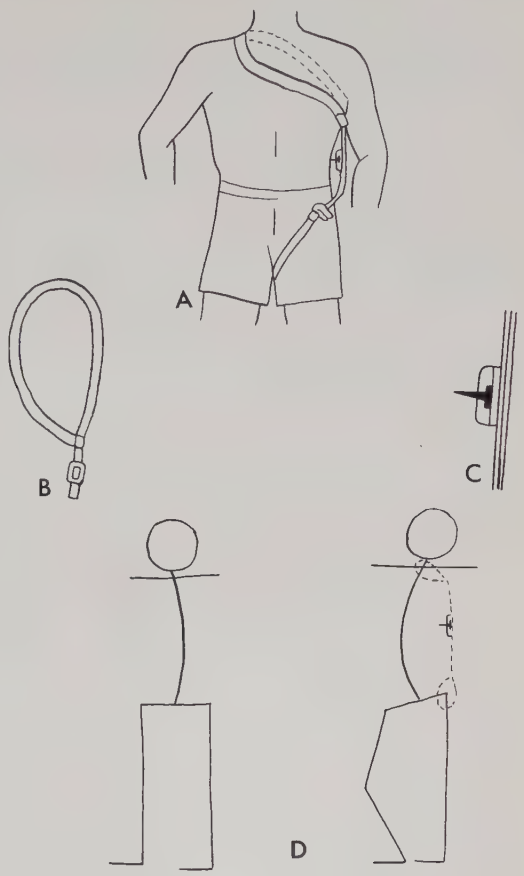

Figure 7. *A*, The harness as it fits on the patient's body. The side strap is *always placed on the convex side of the curve.*

B, This harness is made of 1-inch web belt or strap or any similar material. The neck-shoulder loop and the groin loop are sewed together, leaving one end of the strap protruding downward or upward as the case may be. On the end of this strap extension is a buckle. The side strap is likewise 1-inch web belt and is attached above and below by means of the buckle, so that the strap may be moved or adjusted upward or downward and so that it can be tightened or loosened.

C, The side strap with a ¼-inch piece of felt either sewed, cemented or glued to it. A flat-headed tack is placed on this little square of felt and another ¼-inch piece of felt is thrust down over the tack, leaving about 1 mm. of the tip of the tack protruding through this second piece of felt. These little pieces of felt may be attached to each other and to the side strap by sewing them, gluing them or holding them together with moleskin tape. The tip end of the tack should be sharpened with a file before you apply it to the side strap. The felt-tack device is, of course, on the inner surface of the side strap.

D, These stick men diagrammatically show how the harness causes a patient to lean toward the convexity and tilt his pelvis upward on the convex side, thus correcting his curve.

convex side of the curve. Have the child lean slightly sideways, toward the convexity, toward the side strap, and have him tilt his pelvis by standing with all his weight on the leg on the convex side, with the opposite knee bent (Fig. 8), and in that position adjust the side strap so that the sharp tip of the tack is opposite the most prominent fold of skin on that side of the patient's body. Set the side strap in the buckles above and below, draw a little pencil mark on the strap and instruct the patient always to replace the harness with the side strap in the exact location when he takes it off to take a bath.

As long as he wears the harness brace the patient will not stand naturally, nor will he lean toward the concavity of the curve, thus accentuating the curve, because the sharp-pointed tack is drawn up against the skin on the side of his body when he does so. It sticks him and he reflexly leans the other way, toward the tack, drawing his side away from the tack, and exerting a corrective force on the curve.

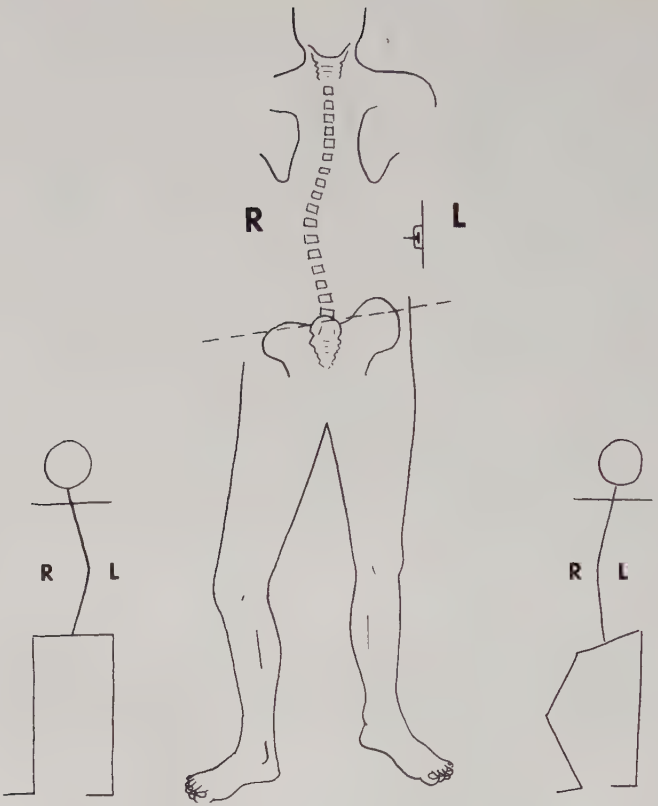

Figure 8. How a patient who is wearing the scoliosis harness should stand when he stands still—with all of his weight on one leg (the leg on the convex side), the opposite knee bent but the foot on the floor. This tilts the pelvis upward on the convex side and downward on the concave side. The pelvic tilt straightens or overcorrects the spine curve. If he stands this way, the tack will not stick him and he has a constant corrective force on this curve. The little stick men show how tilting the pelvis straightens or overcorrects the curve.

He wears the scoliosis harness night and day because the spine grows night and day.

Thus all day long and all night too he has a correcting force on his spine. He sits, stands, walks, and sleeps in such a way that a corrective force is constantly present on his growing spine, making it grow straight instead of crooked.

You should see the child one week after the harness is first applied and about every 30 days thereafter for two or three times because the tip end of the tack sometimes gets bent down so that it does not stick the child, or the child may start putting a pad between the tack and his body. You must check and have the parents check to be sure that the sharp tip of that tack protrudes one millimeter beyond the surface of the little felt pad, so that if the child stands straight or leans the wrong way the sharp tip will stick the side of his body, and make him lean the way you want him to lean.

Also teach the child, if he does not learn it reflexly, to tilt his pelvis while standing with the knee on the concave side slightly flexed (Fig. 8).

Be sure to explain to the parents that it is not the force, pull, or tightness of the straps that holds the child in a correcting position; it is the reflex action of the sharp tack sticking the side of the body that is important.

The only irritation of the skin that I have ever seen is a slight erythematous area about one or two centimeters in diameter.

Sometimes within a few months' time the spine is corrected completely; sometimes it takes as long as two or three years. You have broken up the patient's habitual scoliosis stance and the spine will grow straight.

To check whether the curve is completely corrected, of course, you make an x-ray, with the patient *standing naturally,* with his weight equally distributed, knees straight, and no elevation. If the spine is straight, then remove the scoliosis harness.

Keep the child under observation. Have him come back every six months and make an x-ray and if for another year or so the spine stays straight, you can dismiss him from further care, but if the curve should begin to recur, you can reapply the harness and thus *control growth of the spine*, preventing a severe curvature from ever forming.

Sometimes when a child has worn the scoliosis harness for several months he will become *conditioned* to standing and sitting and walking in this correcting position induced by the reflex action of the tack in the side strap. If the child continues this conditioned response of standing and sitting and walking while leaning to one certain side after you discontinue the use of the harness, then you must exert definite efforts to break that habit, because he might develop a curve in the opposite direction. This happens only rarely.

Do not try to use this scoliosis harness on a patient with a fixed curve because it will not work.

CONDITIONED RESPONSE–LOW BACK–ABDOMINAL STRENGTHENING POSTURE BRACE

Figure 9 shows a brace that is designed to make a patient hold his abdominal muscles contracted. He will, while wearing this brace, constantly hold his abdominal muscles tight. In doing this he flattens his lower back, thus diminishing or correcting a swayback posture. When the skin of the abdomen touches the two little sharp-pointed tacks in front of the brace, the patient reflexly tightens his abdominal muscles to get away from them. As he keeps them tight all day long in reflex response to the sticking sensation from the tacks, the muscles become stronger and the patient acquires the habit of constantly "sucking in his guts." If he does this long enough and the muscles become strong enough, a swayback can be flattened and potbelly droop eliminated.

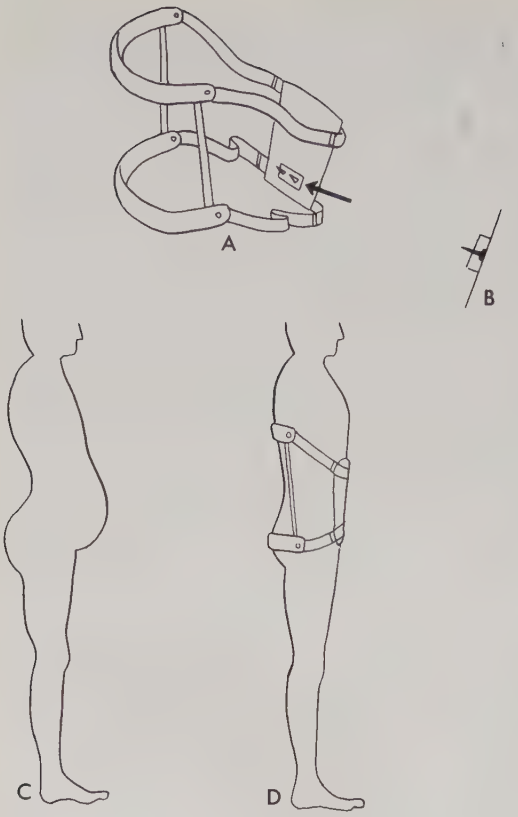

Figure 9. *A*, The metal part of this brace consists of an upper posterior low-chest band, a lower pelvic band and a side bar on either side connecting these two bands. The front or apron is attached to the brace with straps and buckles. Note the little, sharp, protruding tack tips (small arrow) on the inner aspect of the abdominal apron. There is one on either side of the midline. These sharp tips are to touch the patient's protruding *lower* abdomen.

B, Construction of the conditioned response mechanism. A flat-headed tack is thrust through a small square of felt, thick enough that only 1 mm. of the tip of the tack protrudes through it. This felt-tack piece is cemented or sewed to the inner aspect of the abdominal apron.

C, The usual type of "potbellied" man who has gotten into the habit of letting his abdominal muscles stay relaxed and thus has developed a "pot belly" and a swayback posture.

D, The brace reflexly makes the man hold his abdominal muscles tight. By doing that he flattens or lessens the swayback, thus correcting his posture.

Indications for the Use of This Brace

There are two indications:

One is a developing roundback, swayback deformity in a swayback child. The abdomen protrudes forward, and there is a marked swayback and a *beginning roundback deformity that has not become fixed.* A conditioned response brace will cause the child to hold the abdomen in and as a result of this constant exercise, the abdominal muscles will become strong enough to flatten the swayback condition. Held in a correct position, the back will grow normally instead of into an abnormal fixed swayback deformity. Usually the roundback part of the deformity corrects itself spontaneously along with the assumption of the proper low back position.

The second indication is a developing "potbelly" in older or middle-age men who are beginning to develop vague abdominal symptoms and an ache in the lower back—not a pain, just an ache. These patients have a desire to stand straight, like a soldier; "like I did when I was a boy," many say. The application of a conditioned response brace to these patients will do the same thing it does for a child except that it takes a little longer to get a good result.

CELLULOID OR SILASTIC BACK BRACES

This brace does not have any metal in it. It is made entirely of a plastic material or celluloid (Fig. 10). Many of them now are made of fiberglass or a material called Silastic rather than celluloid, but the celluloid ones are still the best, because they hold their shape longer, are more rigid, stronger, and less irritating, and they do not crumble at the edges.

A celluloid brace may be full length, that is, reaching as low as the pubic bone in front and as high as the suprasternal notch above. In the back, it goes down to the top of the gluteal cleft and upward as high as between the middle of the shoulder blades. It is curved down under the armpits for comfort and upward in the lower front part on both sides, so that when the patient sits down, the front of his thighs do not press upward against the brace.

A half length brace covers only the lumbar spine. It can be made to hold the spine in extension or in flexion or straight, but most often it is shaped to hold and support the spine in a straight natural erect position.

The only way you can secure a celluloid brace is to make a plaster-of-paris model of your patient's body and send the cast to the brace maker. Apply a body size stockinette directly against the skin of the patient's body. Cut small holes in the stockinette for the arms to protrude through and leave part of the stockinette going up over the shoulder. Let the stockinette extend about half way to the knee.

Have the patient stand in the position you want his back to be immobilized in. Moisten the end of an indelible pencil with a wet sponge and then mark the stockinette, top and bottom, front and back, the exact shape of the brace you want.

Now apply the cast. After it sets, cut it down the middle in front, spring it open, take it off the patient, push the cut edges together and wrap a bandage about the cast to hold those edges approximated and send it to the brace shop.

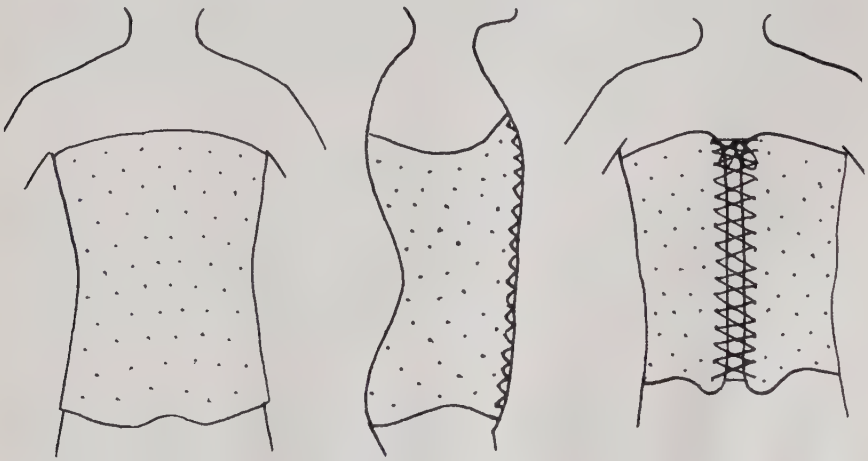

Figure 10. The celluloid or Silastic back brace.

The brace maker seals this cast in front where it has been cut, and then pours plaster-of-paris cream down into the cast, filling it completely.

After the liquid plaster that has been poured into the body cast has set, then he peels the body cast off, leaving a mold that is an exact duplicate of the patient's body. On that mold or model there are markings from the indelible pencil marks made on the stockinette.

The brace maker then wraps around this model layer on layer of bandage soaked with celluloid that has been dissolved in acetone. After he has made the brace of a uniform thickness, and it is approximately one sixth of an inch thick, or maybe a little more, depending on the size of the brace, he takes the celluloid brace off the model, trims it to the desired shape, covers the edges with leather, cuts part of the front out and puts a leather tongue across the front, and makes holes in the edges so that a shoelace type of lacer can be used to hold the brace on the patient.

Indications for the Celluloid Brace

The celluloid type of brace is usually used on a patient who has a weak decalcified spine or painful spinal arthritis and is going to have to wear a brace for the rest of his life. A celluoid brace is light and it fits the patient's body exactly because it was made from a plaster model of it. Because it is thin, ordinary clothes can be worn over it and it doesn't show.

This brace is usually more expensive than an ordinary chairback type of back brace, it is harder to get and it takes much longer to have one made.

The celluloid brace, either long or short, does the same thing that a chairback brace does. It immobilizes the spine in a neutral, natural, straight position, although if a doctor wants to, he can make the model with the patient leaning forward or backward, making a flexion type or hyperextension type of brace, but these are not very satisfactory. Most satisfactory is the long celluloid brace reaching from the pelvis to the armpits and designed to hold the spine immobile in a straight and natural position. It is strong, it is thin, it immobilizes well, and it will last a lifetime with ordinary care.

SACRO-ILIAC BELTS

This is a relatively narrow belt that usually has a pad in the back but not always (Fig. 11,*A*). *It fits below the iliac crest and above the greater trochanter* (Fig. 11, *B*). When it is strapped on tightly it prevents movement through the sacro-iliac joints by squeezing them together.

Indications for Use

Sometimes after a pelvic fracture is healed, there remains an abnormal degree of mobility in one or both sacro-iliac joints, and when the patient walks a lot, the abnormal mobility causes pain directly over

the posterior-superior iliac spine and just below it. A sacro-iliac belt will eliminate the abnormal mobility and stop the pain.

The most common use, though, is for the pain from rheumatoid arthritis involving the sacro-iliac joints. These joints are rather stable ones, but there is a small amount of movement in them which in the early stages of arthritis is painful. A sacro-iliac belt tightly squeezing the pelvic bones together will stop all movement in the sacro-iliac joints, and thus lessen the pain.

The patient should not make the mistake of wearing the sacro-iliac belt too low over the greater trochanter area—it will not do any good there. If the sacro-iliac belt is worn too high over the rim of the iliac crest, it will not compress the sacro-iliac joints together. It should be worn midway between the greater trochanter below and the iliac crest above and it should be as snug as possible (Fig. 11,*B*).

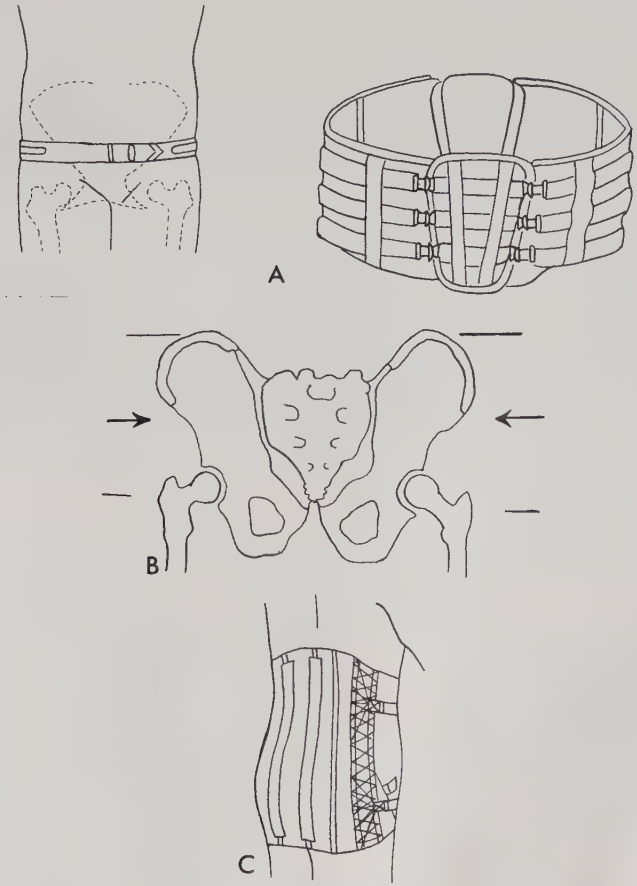

Figure 11. *A*, Two ordinary types of sacroiliac belts. One is just as good as the other. *B*, Pelvis, showing where the center of the pressure should be to compress the sacroiliac joints together. *C*, Lumbosacral supports.

LUMBOSACRAL CORSET SUPPORT

This is actually a garment rather than a brace; it is a corset much like women wear, but it has two and sometimes more semiflexible or semistiff stays in it (Fig. 11,*C*). Theoretically it is used to support and immobilize the lower back, but practically it does not do much immobilizing. I have made side view x-rays with the back flexed as far as possible and bent backward as far as possible with the patient wearing this corset brace; when I compared them with the same views taken without the brace I found very little difference at all in extension and only a slight amount in flexion. The effect of the brace is more psychological than mechanical.

The brace can be used as a reminder—the patient is not so likely to bend his back because the brace reminds him not to do so.

These corset braces are easier to put on while lying down.

Indications for the Lumbosacral Corset Brace

These are usually used on women who wouldn't wear a chairback or a flexion type of back brace if you prescribed one. There are some women who state that their stomachs are sore so that if anything presses over the front of the abdomen, they will have "constipation" or "gas" or various other complaints; regardless of how much back pain they have these women will not wear a metal brace, but many will wear a corset-like brace. Since these women are not doing heavy labor anyway, a corset-like lumbosacral support will often suffice.

Occasionally one may be prescribed for a man who has a mild or moderate amount of back pain and who does not do heavy work.

A lumbosacral corset brace support is a rather poor substitute for the chairback back brace. It is absolutely no good at all when a flexion brace is indicated, nor is it of any value in spinal fractures, chronic spinal arthritis, and postural abnormalities.

It is less expensive than the other braces and it does not show under clothing but it does not do much good either.

HOW TO MEASURE A PATIENT FOR EACH OF THESE BRACES

If there is a brace shop in the town where you live, you can call and have the brace maker come to your office and measure the patient for the brace you prescribed.

If the brace man is busy and cannot get away, then give the patient your prescription indicating the type of brace he needs and have him go to the brace shop and be measured.

If the brace shop is in another city, then the next time you are there stop in and get acquainted with the brace maker, and tell him that you are going to order back braces from him from time to time. He will give you some measuring data, usually a sheet of paper with the human figure sketched on it and the notations as to where you are to measure for each type of brace.

Listed here are the measurements that you can make if your patient cannot go to the brace shop and if the brace man cannot come to your office. You can send your brace order plus these measurements to the brace company, which will send the brace to you so that you can apply it to the patient in your office.

Measurements for the Chairback Back Brace

1. Circumferential measurement around the chest 2 inches below the nipple.
2. Waist circumferential measurement at the navel level.
3. Pelvic circumferential measurement half way between the greater trochanter and the iliac crest.
4. From the 7th cervical spinous process to the top of the gluteal cleft.

Measurements for the Flexion Back Brace

1. Circumference of the chest (about 4 inches below the nipple line).
2. Circumference of the waist (at the navel line).
3. Pelvic circumference (one half the distance between the greater trochanter and the crest of the ilium).
4. Back, from the 7th cervical spinous process to the prominence of the sacrum (gluteal cleft).

Measurements for the Taylor Type Back Brace

The measurements are the same as for the chairback back brace. In addition, indicate how much hyperextension you want by a small rough sketch on paper. When the brace arrives you can increase or decrease the degree of hyperextension by carefully bending the back upright bars over the back of a chair.

Measurements for the Jewett Type Back Brace

Write to the company* and get them to send you the measurement chart. A brace maker can make a Jewett type brace, but frequently he will order it from the manufacturer.

The measurements he will need to make the Jewett type of brace, if he makes it himself, are:

With the patient lying on his back with his back in hyperextension:

1. Measure from the suprasternal notch to the symphysis pubis—straight line measurement.
2. Measure from the navel to the symphysis pubis.
3. Measure the chest circumference at the widest point.
4. Measure the waist circumference.
5. Measure transversely from one anterior superior iliac spine to the other.
6. Measure the pelvic circumference midway between the greater trochanter and the crest of the ilium.

The brace maker may be more familiar with the Baker type of hyperextension brace, and if you and he prefer, he can make that one from these measurements.

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*Florida Brace Corporation, 601 Webster Avenue, Box 1299, Winter Park, Florida 32790.

Measurements for the Ordinary Scoliosis Brace

1. Circumferential measurement of the pelvis halfway between the greater trochanter and the crest of the ilium.
2. Circumferential measurements of the upper chest with the tape as high as you can easily get it under the armpits.
3. The length of the left side between the lower measurement level and the upper measurement level.
4. The length of the right side between the lower measurement and the upper measurement level.
5. The length from the 7th cervical spinous process (the most prominent one) to the top of the gluteal cleft.
6. Drop a plumb line from the 7th cervical vertebra and see whether it rests directly in the midline of the pelvis, or to the right or left of the midline (gluteal cleft). If it is off center, measure how far off and indicate to which side.
7. Draw a small rough sketch of the patient's torso, indicating the hump with an oval ring.

Measurements for the Other Braces Described

For the *Conditioned Response–Low Back– Abdominal Strengthening Posture Brace* the measurements are the same as for the chairback back brace.

For the *Conditioned Reflex Scoliosis Harness*, make an angular or loop measurement around the groin and around the neck and shoulder and the length of the side strap. Any brace maker or anyone who has a sewing machine can make this brace. Figure 7 will give an idea of how it should look.

For the *Celluloid or Plastic Brace*, apply a cast to patient's body, remove it, and send the cast to the brace company as described in the previous discussion of this brace.

For the *Sacro-iliac Belt*, make a circumferential measurement halfway between the greater trochanter below and the iliac crest above.

The *Lumbosacral Support*. These supports come in various sizes. The brace maker chooses the size nearest the patient's pelvis measurement and adjusts it to fit. If you order one, make a circumferential measurement around the patient's pelvis, halfway between the greater trochanter below and the iliac crest above.

BACK BRACE ADJUNCTS

There are two or three tricks that can be reserved for special patients in whom a little extra attention seems to be indicated.

Keep in mind that the primary purpose of wearing a back brace is to relieve back pain. Any one of the following additions to a back brace brace greatly enhances its pain-relieving qualities. I have used all of these at various times during the last few years and have found them quite satisfactory.

Pressure Pad Principle

Secure a fairly thick pad of felt about 4×5 inches in size. Attach elastic straps to it, and place it on the brace in such a way that when the brace is on, firm constant pressure is made by this pad over the area

of maximum pain (Fig. 12,*B*). Pressure alone directly over a painful area helps relieve pain.

Pressure Pad Plus Counterirritation

This same pressure pad may be used with an extra piece of Sani-sheet fixed to the anterior surface of it with four snaps (Fig. 12,*A*). The Sani-sheet may be covered with a counterirritant salve, snapped onto the front of the pad and the pad placed over the painful area but directly against the bare skin. Sani-sheet is used because the salve will not penetrate it and soil the felt pad. It is fixed with snaps to the pad because, on some days, the patient may not want to use the salve and he then can remove the Sani-sheet cover.

In this instance the patient feels both the pain-relieving effect of local pressure plus counterirritation.

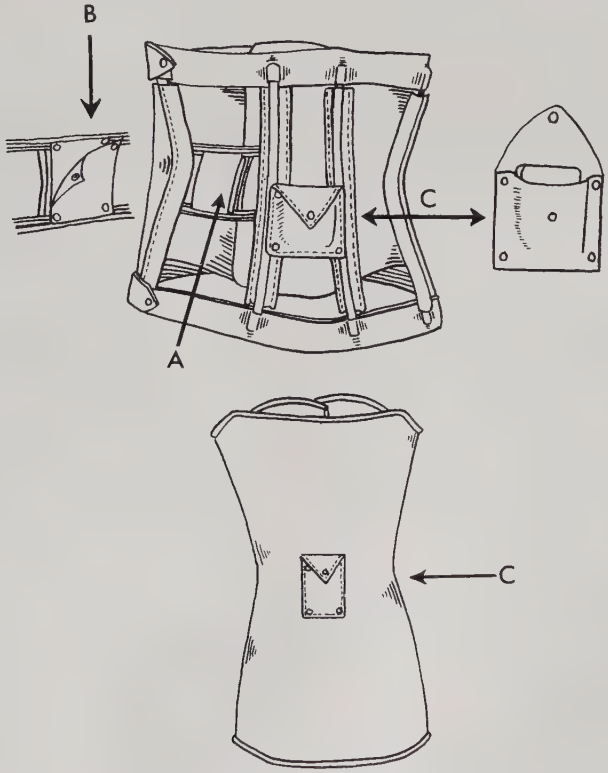

Figure 12. *A*, Pressure pad in place between the side bar and one of the back bars of the brace. It is held in place with two elastic straps and it is thick enough that it will produce relatively firm pressure over the patient's back at its most painful point. The patient will locate this spot for you.

B, The piece of Sani-sheet is attached to the front of the pressure pad with four snaps.

C, The leather pocket with the heater inserted in it is affixed to the lower central portion of the back brace. It is in the central portion of a celluloid brace.

Heat Principle

A small leather pocket is made and is placed on the brace as in Figure 12,C, so that it lies over the painful part of the back. A pocket warmer is placed inside to furnish heat to the patient's back over the most painful site. The amount of heat may be regulated by placing one or two or more pieces of cardboard between the heater and the skin.

The pocket warmer is perfectly safe because there is no open flame in it, and it stays hot for 8 to 10 hours. It may be secured from any sporting goods store.

In this instance pain relief occurs because of the brace, because of the heat, and because of the localized pressure made by the heat unit.

WHEN THE PATIENT GOES BACK TO WORK

If your patient has had a back injury and has recovered, with or without a brace, here are some instructions to give him before he goes back to work.

If the patient follows these instructions, he will be much less likely to reinjure his back.

Tell the patient to read the instructions thoroughly, three or four times or more.

INSTRUCTIONS TO THE WORKING PATIENT ON PROTECTING HIS BACK

Even though you have made a complete recovery and your back seems to be well you must remember that a back once injured may be injured again. It may be more easily injured the second time than the first time, therefore you must learn how to use your back in such a way as to avoid putting undue strain on it. You should do these things for the rest of your life.

Most of these instructions have been collected over a period of years from patients who have had injured backs and who have gone back to work, but have learned how to protect their backs and by doing these things they have been able to stay on the job.

Read these instructions several times—memorize them. Practice them purposefully *until it becomes a habit* to carry out these particular directions at all times. If you do this, you will be much less likely to reinjure your back.

1. If you pick up something from the floor, do it by bending your knees and hips and not your back. Keep the back as straight as you can, naturally straight, not rigidly straight.

2. To lift anything that is heavy from the floor, bend your knees and hips, squat down, firmly grasp the object, and then straighten your legs.

Another good trick to remember when lifting something from the floor is: Squat down, grasp the object, *then rest your bent elbows against your thighs.* Lift the object by bending the elbows and *pull the object against your body,* and then straighten the knees and hips. Keep the object as close to your body as possible while you lift it.

3. When you carry a heavy object keep it as close to your body as possible, not out several inches in front of you. Keep your back straight, or slightly flexed *but don't bend backward* (slightly flexed means bent forward a little bit).

4. When you are carrying a heavy weight and you want to set it down, lean forward slightly, then bend your hips and knees and put the object straight down, not out in front of you.

5. If, for a while, you have to do some work down on the floor, get down on your knees to do it. If it is a hard floor and it hurts your knees, get some knee pads. Get down on both knees or, if you prefer, on one knee with the other knee bent, but in any instance keep your back straight. Working in a leaning forward

position *while your knees are straight* for a considerable period of time will inevitably put a great deal of strain on your lower back.

6. Be sure your feet are firmly fixed when you start lifting something so that you will not slip. Spread your feet apart a little for more stability. Sometimes place one foot forward and away from the other one – a "spraddle-legged walking position."

7. *Avoid hyperextending the back* (leaning backward). This always is very likely to bring on pain.

8. Be sure your hands are firmly fixed on the object you are going to lift so your hands won't slip. Also, if you are lifting something heavy with somebody else, be sure the other fellow has his hands firmly fixed, because if he drops his end, it throws a terrific jerking strain on your back.

9. Never lift something that is beyond your strength. If the object is heavy, get help. Don't try to do it by yourself. If in your job you are constantly lifting heavy objects, never lift anything that weighs more than one third of your body weight. If you lift something only occasionally, then it is safe to life something that weighs half as much as your weight, but never by yourself, unaided, lift anything that weighs more than half your body weight. Most important of all, *while lifting something don't bend backward.*

10. Do not lift with a quick jerky movement. *Lift slowly.*

11. *Never twist your back while holding a heavy object.* If you are holding any sort of weight in your arms and you want to put it down to your left or right, then *turn your body by moving your feet and not by twisting your back,* before you put it down.

12. If you are standing near a solid object, for example, a barrel, and you have to lean down and pick up something out of the barrel, and thus apparently can't bend your knees, then turn sideways to the right or left and lean down and pick it up by bending your knees and not your back. Alternate between twisting to the left and to the right.

13. If you have to lift a *large* heavy object, *with some other person*, you should stand in front of the object. Back up to it. This puts less strain on the back than leaning forward to carry such an object.

14. If you have been working in a leaning forward position or even if you have done nothing but lean forward over a sink or lavatory, as in brushing your teeth, then when you straighten up, first of all bend your knees, slowly straighten up with your hands on the lavatory and then straighten your knees. This will not put as much strain on your back as straightening up through the spine with your knees straight.

15. A simple thing like quickly or awkwardly getting up out of a chair can put an abnormal strain on your spine, but if you do it as explained here, you will avoid this strain.

If you are sitting in a chair that has arms, slide forward close to the front edge of the chair and push yourself up with your arms. If you are sitting in a chair that does not have arms, slide over to the side edge of the chair. If it is the left side put your left foot backward then straighten both knees. In doing this you will find yourself standing erect without having bent your back. If it is the right edge of the chair, of course, thrust your right leg backward.

16. If you have been working while sitting on the floor, here is the way to get up: If you have been sitting with both legs out in front of you, thrust your stronger leg (the right one if you are right handed) behind you while lifting your body slightly with your hands against the floor. Then bend the other knee to a right angle. You are now in a squatting position, with one knee behind you. Now straighten both knees and you find yourself in an erect position without having put a strain on your back.

17. Avoid sleeping on your stomach. If you must do it, put a pillow under your abdomen to flatten your back.

Remember that you only have one back; take care of it.

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